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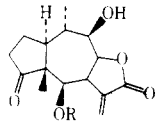
(22) All constituents, including some new helenanolides, were active in the cytotoxicity and PS-388 assay.
(23) $J_{1,5}$ of gaillardin is reported[20] as 12 Hz, whereas $J_{1,5}$ of the common cis-fused guaianolides, whether lactonized toward C-6 or C-8, hovers in the 9–11 Hz region.
(24) To these might be added three other congeners,[14,18] fastigilins A, B, and C (**8a, 8b,** and **8c**), on the basis of the Cotton effect associated with their cyclopentenone function.



8a, R = senecioyl, 11,13-dihydro
b, R = tigloyl, 11,13-dihydro
c, R = senecioyl

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(28) The values of $J_{7,8}$ and $J_{8,9}$ in baileyin differ somewhat from those exhibited by the 4,5-epoxide of frutescin, another melampolide with a lactone ring closed to C-8, but presumed to be cis.[12] Chemical shifts in the two epoxides are not strictly comparable because of the presence in frutescin of an aldehyde function on C-10 which, for one, is closely responsible for paramagnetic displacement of H-9b. The presence of the α,β-unsaturated aldehyde in frutescin also beclouds interpretation of the lactone Cotton effect near 250 nm (negative for frutescin epoxide,[12] positive for baileyin[14]) which would normally be taken as evidence for opposite stereochemistry at C-8, i.e., **5a** for baileyin.
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Catalytic Transfer Reduction: Scope and Utility

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Catalytic transfer reduction has been reviewed recently.[1] In an attempt to extend the scope and utility of this reaction, we have demonstrated its applicability to the complete reduction of aromatic aldehydes and ketones.[2] In this paper we wish to elaborate on this topic. Specifically, we have investigated the interception of the intermediate benzylic alcohol as the acetate, the reduction of some more complex carbonyl compounds, and the relative effectiveness of a variety of donor compounds.

Table I. Partial Reduction of Aromatic Aldehydes[a]

aldehyde	product (% yield)[b]
p-anisaldehyde	*p*-methoxybenzyl acetate (83)
2,6-dimethylbenzaldehyde	2,6-dimethylbenzyl acetate (77)
p-isopropylbenzaldehyde	*p*-isopropylbenzyl acetate (81)
α-naphthaldehyde	1-naphthalenemethanol acetate (68)
benzaldehyde	benzyl acetate (72)

[a] Reaction conditions: 0.5 g of starting material, 5 mL of cyclohexene donor, 100 mg of 10% Pd/C, 50 mg of anhydrous $FeCl_3$, 1.0 mL of acetic anhydride, reflux 12 h maximum. [b] Yield determined gas chromatographically.

Table II. Reduction of More Complex Aryl Ketones[a]

ketone	product (% yield)[b]
cyclopropyl phenyl ketone	*n*-butylbenzene (100)
4-benzoylbutyric acid	5-phenylpentanoic acid (60)
trans-1,2-dibenzoylethylene	1,4-diphenylbutane (68)
6-methoxytetralone	6-methoxytetralin (33) 2-methoxynaphthalene (20)
4-chloroacetophenone	ethylbenzene (100)

[a] Reaction conditions: 1.0 g of starting material, 10 mL of limonene donor, 400 mg of 10% Pd/C, 100 mg of anhydrous $FeCl_3$, reflux 4 h. [b] Yield determined by gas–liquid chromatography.

Trapping of Intermediate Benzylic Alcohols. During the reduction of *o*-acetylbenzoic acid and salicylaldehyde, it was noted that intermediate lactones were formed, which remained relatively stable to further reductions. Accordingly, reduction of aromatic aldehydes and ketones was carried out in the presence of acetic anhydride. This allowed the trapping of intermediate benzylic alcohols in the form of acetates, starting with a variety of aromatic aldehydes. The results are given in Table I. It was not possible to trap intermediates from aryl ketones. Presumably, the rate of hydrogenolysis of secondary benzylic acetates is competitive with the initial reduction. On the basis of these results, catalytic transfer reduction of aromatic aldehydes may be seen as a useful alternative to hydride reduction, provided other groups such as nitro or halo substituents are not present since these groups are readily reduced.

Reduction of More Complex Aryl Ketones. In a further effort to determine the structural limits for catalytic transfer reduction, a variety of aryl ketones were selected for study. The results are given in Table II. It was noted during the reduction of phenyl cyclopropyl ketone that the initial reaction was cleavage of the cyclopropyl ring to form phenyl *n*-propyl ketone. This was followed by quantitative reduction of the carbonyl group. 4-Benzoylbutyric acid and *trans*-1,2-dibenzoylethylene were reduced to the expected products without incident. During the reduction of 6-methoxytetralone, 2-methoxynaphthalene was also formed. Not unexpectedly, the initially formed 6-methoxytetralin partly dehydrogenates under the reaction conditions. Ethylbenzene was formed quantitatively during the reduction of 4-chloroacetophenone, indicating the ease of hydrogenolysis of aromatic halogen under the reaction conditions employed.

Comparison of Donor Compounds. In the course of these studies, the relative reducing capacities of a variety of donors

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Table III. Hydrogen Donating Abilities of Hydrocarbons[a]

hydrogen donors	% products[b] ethylbenzene[c]	octane[d]	toluene[e]
d-limonene	100	100	80
α-phellandrene (tech)	96	99	59
tetralin	28	51	55
cis-Δ^4-tetrahydrophthalic anhydride	23	57	41
bicyclo[4.3.0]nona-3,7diene	49	43	94
4-vinylcyclohexene	6	30	80
9,10-dihydroanthracene	2	70	40
isopulegol	9	16	16
l-carvone	6	7	14

[a] Reaction condition: 0.07 mol of donor, 0.01 mol of acceptor, 400 mg of 10% Pd/C, 100 mg of $FeCl_3$(anhydrous), reflux for 3 h. [b] Yields determined via gas–liquid chromatography. [c] Acetophenone as hydrogen acceptor. [d] 1-Octene as hydrogen acceptor. [e] Benzaldehyde as hydrogen acceptor.

were investigated with a view toward providing more active donors. In principle, a large variety of hydroaromatics could be used, but our principal concern was the employment of readily available donors.

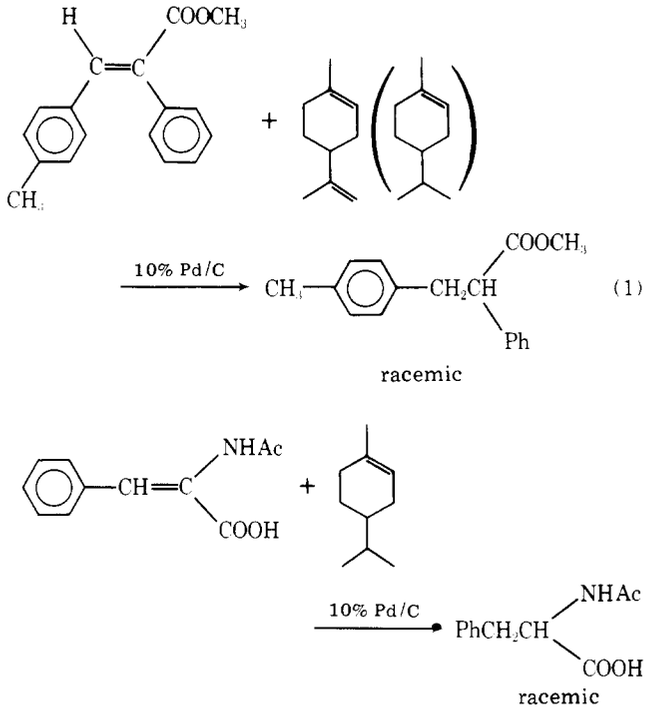
It will be noted from Table III that limonene and α-phellandrene are the best general donors, useful both for the reduction of alkenes as well as for aromatic carbonyl compounds. Bicyclo[4.3.0]nona-3,7-diene and 4-vinylcyclohexene are also useful for the reduction of aromatic aldehydes. It must be remembered that decarbonylation is a competitive process in the reduction of aldehydes, and donors active at lower temperatures are preferred. Carvone is not an effective donor, possibly because aromatization can take place readily by intramolecular hydrogen transfer and enolization.

The mechanism of intermolecular hydrogen transfer is complex, and a careful reexamination of the catalytic dehydrogenation/disproportionation of *d*-limonene in the presence of palladium catalysts indicates that a variety of isomers derived from these processes are present shortly after reaction is initiated.[3] For instance 1-*p*-menthene, available from other sources in more substantial quantities, is also quite active as a donor. In view of these possibilities, we do not wish at this point to speculate further on the relationship of donor structure to reducing ability since it is clearly possible that a transient intermediate species is in fact the most effective donor.

In any event, it appears that catalytic transfer reduction of aromatic aldehydes and aryl ketones can be used as an alternative in many cases for the Clemmensen or Wolff–Kishner methods. In the case of aldehydes, it is also possible to halt the reduction at the alcohol stage by trapping with acetic anhydride.

Asymmetric Induction. It has been pointed out that there is evidence for the idea that catalytic transfer reduction is not simply ordinary catalytic hydrogenation with an alternative hydrogen source.[1] If the donor compound is involved directly in the reduction mechanism, there exists the possibility that asymmetric induction may occur with an optically active donor and a suitable acceptor.

Several systems were explored for this purpose. For instance, the methyl ester of 2-phenyl-3-*p*-tolylpropenoic acid was reduced with both (+)-limonene and (+)-1-*p*-menthene according to eq 1. Although the reduction proceeded smoothly in good yield, no optical activity was found in the resulting product. A second study employed α-acetamidocinnamic acid as acceptor and (+)-menthene as donor. This acceptor has been successfully reduced to an optically active product using asymmetric homogeneous catalysts.[4] Again, however, no optical activity was observed in the product *N*-acetylphenylalanine.

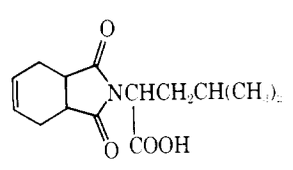


(1)

In order to maximize steric effects, (±)-α-pinene was also reduced with (+)-limonene. No optical activity was found in the products.

Terpene donors such as limonene undergo complex transformations during catalytic hydrogen transfer due to disproportionation. Accordingly, the disproportionation of (+)-limonene was reinvestigated.[3] These studies showed that (+)-limonene lost its optical activity in the presence of palladium in a matter of 20 min. A complex mixture of disproportionation products is formed, which contains at least eight components, including several menthenes in principle capable of optical activity. However, the decline in optical activity with time corresponds directly to the remaining concentration of limonene. It thus appears that any potential use of limonene as an optically active donor is limited to a short time period. Furthermore, we can conclude that there is no asymmetric induction during the disproportionation of (+)-limonene.

As a final test, an optically active transfer reagent was synthesized from L-leucine and 1,2,5,6-tetrahydrophthalic anhydride (I). This reagent was again tested with methyl 2-phenyl-3-*p*-tolylpropenoate. No optical activity was found.



I

We are thus forced to conclude that catalytic transfer reduction does not pass through a critical conjunction of donor, acceptor, and catalyst capable of inducing asymmetry.

Experimental Section

General Conditions for the Transfer Reduction of Aromatic Aldehydes and Ketones. The aldehydes and ketones were generally purified by distillation or recrystallization prior to use. In one case it was necessary to use the bisulfite addition product for purification.

The donors are generally used directly as available commercially. In the case of the terpene donors especially, it was not found practical to effect a higher degree of purification.

The 10% Pd/C catalyst was of commercial origin (Engelhard, Ventron).

Identification of products was made by collection of samples using gas–liquid chromatography (15 ft × ¼ in. 152 DEGS or SE-30) and by IR and NMR spectra.

Benzyl Acetate by Transfer Reduction. Freshly distilled benzaldehyde (20 mL, 0.196 mol) was combined with 50 mL of cyclohexene, 2.0 g of 10% Pd/C, 20.45 mL of acetic anhydride, and 200 mg of $FeCl_3$ and refluxed for 4 h. The mixture was filtered to remove the catalyst and fractionally distilled to give 17.6 g (60%) of benzyl acetate, bp 104 °C (aspirator vacuum).

Transfer Reduction of (+)-α-Pinene. A mixture of 15.0 mL of (±)-α-pinene, 1.0 g of 10% Pd/C, and 15 mL of (+)-limonene (α^{24}_D +64.3°) was refluxed for 0.5 h. The mixture of pinanes and *p*-cymene obtained after filtration of the catalyst showed no detectable optical activity.

Transfer Reduction of Methyl *cis*-2-Phenyl-3-*p*-tolylpropenoate. Purified methyl *cis*-2-phenyl-3-*p*-tolylpropenoate (300 mg) was dissolved in 3.5 mL of purified (+)-limonene, α^{24}_D +106°, or (+)-1-*p*-menthene, α^{25}_D +70.5°. A 35-mg amount of 10% Pd/C was added, and the mixture was immersed in an oil bath at 195 °C for 6 min. These were the conditions found to be optimum for rapid quantitative reduction. After chromatography on 15 g of silica gel, 248 mg (82% yield) of methyl 2-phenyl-3-*p*-tolylpropanoate was obtained as a viscous liquid. GLC (10 ft 15% DEGS) indicated 100% purity, and NMR and IR data are in accord with the structure. No optical rotation was observed.

Transfer Reduction of α-Acetamidocinnamic Acid. α-Acetamidocinnamic acid (2.0 g) was dissolved in 90 mL of a 70:30 mixture of toluene/1-butanol, 15 mL of (+)-1-*p*-menthene (α^{25}_D +70.5°), and 250 mg of 10% Pd/C. The mixture was refluxed for 51 h at 116 °C. After removal of solvent and recrystallization, 640 mg (31%) of *N*-acetylphenylalanine, mp 140.5–141 °C, was obtained. The product exhibited no optical activity.

***N*-1,2,5,6-Tetrahydrophthalyl-L-leucine[5] (I).** L-Leucine (13.1 g), 15.2 g of 1,2,5,6-tetrahydrophthalic anhydride, 150 mL of toluene, and 1.3 mL of triethylamine were refluxed for 3 h in the presence of a Dean-Stark trap. The toluene was removed using a rotary evaporator, and the resulting semisolid was treated with 100 mL of distilled water and 2 mL of concentrated HCl. After washing with more water, filtration, and drying, 20.6 g (78% yield) of product was obtained. Recrystallization from ethanol saturated with water gave mp 137–138.5 °C. The NMR spectrum is in accord with the expected structure.

Transfer Reduction of Methyl *cis*-2-Phenyl-3-*p*-tolylpropenoate with I. Methyl *cis*-2-phenyl-3-*p*-tolylpropenoate (2.55 g) was combined with 3.0 g of I, 10 mL of toluene, and 500 mg of 10% Pd/C. The mixture was refluxed for 4 h, when NMR indicated complete reduction. After filtration, the solution was extracted with 6 M NaOH, dried, and evaporated to give 2.2 g of an oil which was chromatographed on alumina. Elution with 10% ether in pentane gave 1.3 g of pure methyl 2-phenyl-3-*p*-tolylpropanoate as an oil. No optical activity was observed.

Acknowledgment. The technical assistance of James W. Thill is greatly appreciated.

Registry No.—I, 69705-72-2; benzaldehyde, 100-52-7; acetic anhydride, 108-24-7; benzyl acetate, 140-11-4; (±)-α-pinene, 2437-95-8; methyl *cis*-2-phenyl-3-pitolylpropenoate, 42307-46-0; (+)-1-*p*-menthene, 1195-31-9; methyl 2-phenyl-3-*p*-tolylpropanoate, 69668-17-3; α-acetamidocinnamic acid, 69668-18-4; *N*-acetylphenylalanine, 69668-19-5; 1,2,5,6-tetrahydrophthalic anhydride, 4717-58-2; L-leucine, 61-90-5; *p*-anisaldehyde, 123-11-5; 2,6-dimethylbenzaldehyde, 1123-56-4; *p*-isopropylbenzaldehyde, 122-03-2; α-naphthaldehyde, 66-77-3; *p*-methoxybenzyl acetate, 104-21-2; 2,6-dimethylbenzyl acetate, 62346-87-6; *p*-isopropylbenzyl acetate, 59230-57-8; 1-naphthalenemethanol acetate, 13098-88-9; cyclopropyl phenyl ketone, 3481-02-5; 4-benzoylbutyric acid, 1501-05-9; *trans*-1,2-dibenzoylethylene, 959-28-4; 6-methoxytetralone, 1078-19-9; 4-chloroacetophenone, 99-91-2; *n*-butylbenzene, 104-51-8; 5-phenylpentanoic acid, 2270-20-4; 1,4-diphenylbutane, 1083-56-3; 6-methoxytetralin, 1730-48-9; 2-methoxynaphthalene, 93-04-9; ethylbenzene, 100-41-4; acetophenone, 98-86-2; 1-octene, 111-66-0; octane, 111-65-9; toluene, 108-88-3; α-phellandrene, 99-83-2; tetralin, 119-64-2; bicyclo[4.3.0]nona-3,7-diene, 3048-65-5; 4-vinylcyclohexene, 100-40-3; 9,10-dihydroanthracene, 613-31-0; isopulegol, 89-79-2; l-carvone, 99-49-0; *cis*-Δ⁴-tetrahydrophthalic anhydride, 935-79-5; (+)-limonene, 5989-27-5.

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Asymmetric Chemistry. Comparison of Chiral Phosphines vs. Chiral Phosphinites in the Asymmetic Hydrogenation of Prochiral Olefins Containing a Carboxylic Acid or Ester Group

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The asymmetric hydrogenation of prochiral olefins has been an especially active field of research since Kagan's publication on the use of (−)-DIOP[1] in such reductions.[2,3] A common theme in these reactions has been the use of chiral phosphines as ligands in rhodium-catalyzed reductions. The substrates have frequently included carboxylic acid and/or acetamido groups attached to the olefin moiety. The reduction of olefins not having these groups often resulted in products of lower enantiomeric excess.[2,3]

Recently, Hayashi[4] published the results of asymmetric hydrogenations performed in the presence of a chiral phosphinite, *d-trans*-BDPCP,[5] rather than a chiral phosphine. Interestingly, the products obtained in the presence of this phosphinite proved to have greater enantiomeric excess, in many instances, than products obtained from (−)-DIOP reductions for substrates not containing carboxylic acid or acetamido groups. However, (−)-DIOP still proved to be superior to *d-trans*-BDPCP in the asymmetric reduction of prochiral olefins possessing carboxylic acid and/or acetamido groups. This raised the interesting speculation that chiral phosphines might be better than chiral phosphinites in the reduction of olefins containing a carboxylic acid moiety while the reverse may be true for olefins not containing an acid or acetamido group. Unfortunately, the Hayashi and Kagan ligands are too different in structure to relate their effects entirely to their differences in phosphorus groups.

We sought to determine if one could obtain better asymmetric induction for some substrates with chiral phosphines while the hydrogenation of other substrates may be influenced more by structurally similar phosphinites. Many chiral phosphine ligands have been synthesized by sequences which go through alcohol or diol intermediates. These are usually converted to tosylates or halides which, in turn, can be converted to the diphenylphosphino compounds. These same alcohol intermediates serve as ideal substrates for the preparation of phosphinites. Hence, the same synthetic sequence, with slight modifications, could be used to prepare structurally similar phosphines and phosphinites. The substrates we chose, to test our hypothesis, were olefins containing carboxylic acid moieties and their analogous methyl esters.[6]

For our phosphine–phosphinite pair we wanted to choose a chiral phosphine that had already been investigated in asymmetric hydrogenation. Unfortunately, attempts to prepare a bis(phosphinite) from the diol precursor of DIOP gave thermally unstable species. Likewise, it had been reported that the phosphinite derived from menthol was stable only below −20 °C.[7] Fortunately, the diol precursor of camphos[3e] did react with chlorodiphenylphosphine to produce a thermally

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