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Ethylene in Organic Synthesis. A New Route to Anticholenergic Pyrrolidinoindolines, and Other Molecules with All Carbon-Quaternary Centers via Asymmetric Hydrovinylation

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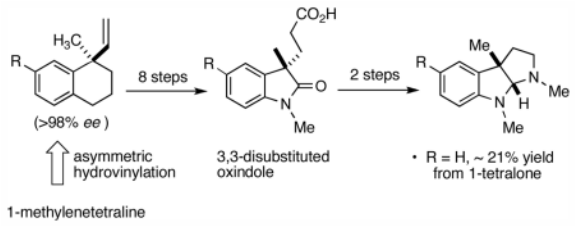
Abstract



The asymmetric hydrovinylation (1 mol % Ni-cat., 1 atm, ethylene, >98% ee) products from 1-methylenetetralines are readily converted into 3,3-disubstituted oxindoles, and subsequently to pyrrolidinoindolines. These hydrovinylation products are also useful for the syntheses of enantiopure benzomorphans.

An all-carbon quaternary center at a benzylic position is a structural motif that is common to many pharmaceutically relevant classes of compounds. These include acetylcholine esterase inhibitor (−)-physostigmine and analogous pyrrolidinoindolines,[1,2] analgesics[3] (+)-aphanorphine and (−)-eptazocine, and cytotoxic, phenolic diterpenoids like (−)-standishinal[4] (Figure 1).

The major challenge in the synthesis of these compounds is the installation of the all-carbon quaternary center, a topic that is of considerable topical interest.[5] In the context of the benzylic quaternary center in the molecules listed above, many of the well-known enantioselective C-C bond-forming reactions have been employed with varying degrees of success. These include the intramolecular Heck reaction,[2h,3l,4b] Ni-catalyzed intramolecular arylcyanation,[2d] Pd-catalyzed intramolecular cyano-amidation,[2e] Mo-catalyzed intermolecular allylation,[2f] Pd-catalyzed intramolecular allylation,[4d] thiourea-[2b,c] or quaternary ammonium-[2i] catalyzed alkylation of an oxindole anion, (*R*)-BINOL-$SnCl_4$-catalyzed [3+2]-cycloaddition,[2a] intramolecular Friedel-Crafts alkylation,[3a] and Pd-catalyzed α-arylation of an enolate.[4e]

Recently our group reported highly enantioselective Ni-catalyzed asymmetric hydrovinylation of α-alkylvinylarenes in which a benzylic, all-carbon quaternary center is generated in high yield and exceptionally high enantioselectivity (Scheme 1).[6] Thus under

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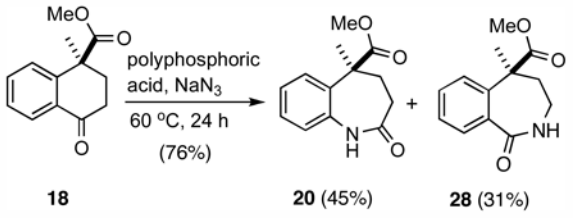
Supporting Information Available. Details of the experimental procedures, spectroscopic and chromatographic data for key compounds. Crystallographic Information Files for structures determined are also included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

optimized conditions, with as little as 1–4 mol % of a Ni(II) catalyst prepared from $[(allyl)NiBr]_2$, a phosphoramidite ligand **8** and a highly dissociated counter anion ($BARF^-$), prototypical substrates **9** and **10** gave the respective adducts **11** and **12** in >98% ee. Despite the modest yield in one of these reactions [**11** (82%), the rest rearranged starting material, 1-methyl-7-methoxy-3,4-dihydronaphthalene)[6a]], this *two-step procedure* from a ketone represents a major improvement over the best routes previously reported for the synthesis of this important class of compounds. For example, **11** has been previously synthesized via stoichiometric oxazoline-directed alkylation (12 steps, 35% overall yield, 99% ee)[3k] or an enzyme-catalyzed desymmetrization of an α,α-disubstituted *meso*-dimethylmalonate (13 steps, 31% overall yield, 97% ee).[3i] Shibasaki et al. prepared a closely related compound using an asymmetric intramolecular Heck reaction (~10 steps, 37% yield, 93% ee).[3l] The compound **12** has been prepared in ~ 51% yield (92% ee) from acetophenone in 4 steps using an enantioselective Cu-catalyzed allylic alkylation, which uses 5 mol % of a catalyst and 3 equivalents of Et_2Zn.[7] As a logical extension of our work, we have been exploring applications of this chemistry for the synthesis of biologically relevant targets, and here we describe an approach to pyrrolidinoindolines. Further applications for the syntheses of benzomorphan analogs (−)-eptazocine and (+)-aphanorphine are also discussed.

An enantioselective synthesis of pyrrolidinoindolines starting from the hydrovinylation product **15** is shown in Scheme 2. This product can be prepared in gram quantities in enantiomerically pure form from 2-tetralone in two steps.[6b,c] The alkene **15** was oxidized with $RuCl_3/NaIO_4$, and the resulting carboxylic acid **16** was protected as a methyl ester (**17)**. Subsequent benzylic oxidation with CrO_3 gave the ketone **18.** Beckman ring expansion of the corresponding oxime **19** and methylation proceeded in excellent yield to give a tetrahydroazepinone **21**, a highly crystalline compound, whose structure was unequivocally established by X-ray crystallography (Figure 2).[9,10]

The high regioselectivity of the successful Beckmann rearrangement of the oxime **21** can be understood in terms of the configuration of the corresponding oxime. At room temperature only one stereoisomer of the oxime, presumably the (*E*)-form, is seen in both ^1H and ^{13}C NMR. Predictably, the corresponding Schmidt reaction,[11] which relies on the intermediacy of a hydroxy-azide, where no such stereochemical constraint is possible, is a much less selective reaction, giving a mixture of benzazepinones **20** and **28** (Eq 1).[12]



(1)

The azepinone **21** undergoes facile acid-induced rearrangement to a more stable oxindole carboxylic acid **22** in excellent yield. 3,3-Disubstituted oxindoles have been used extensively for enantioselective synthesis of pyrrolidinoindolines and several other natural products.[2b–2f 2h 2i 2n] Besides, this class of compounds are important in their own right, and, considerable effort has been expended on their syththeses.[13,14] Curtius rearrangement using diphenylphosphorylazide (DPPA) in the presence of ethanol gives a urethane **23**, which upon reduction with LAH gives, the natural product (−)-desoxyeseroline.[15] This compound is a key intermediate in the synthesis of a number of pyrrolidinoindolines including (−)-

esermethole.[2r] Esermethole has been converted into (−)-physostigmine[2s,16a,b] and (−)-phenserine.[16b]

Finally, we anticipate the intermediates such as **11** (Scheme 1) and **15** (Scheme 2), synthesized in two steps from the corresponding tetralones in nearly enantiomerically pure form, to have broad applicability in the synthesis of benzomorphan analogs. For example, the alkene **11** has been converted into (−)-eptazocine by Meyers[3k] using chemistry developed earlier by Shibasaki.[3l] Likewise, the aldehyde **29** (previous best: 11 steps from 7-methoxytetralone[3k]), easily obtained by oxidative degradation of **11**, intercepts the synthesis of aphanorphine by Shiotani.[3j]

In conclusion, Ni(II)-catalyzed asymmetric hydrovinylations of 1-methylenetetralins provide nearly enantiopure (>98% ee) 1-methyl-1-vinyl-tetrahydronaphthalenes in moderate to high yield (70–82%). This *intermolecular* C-C bond-forming process delivers these valuable intermediates in a significantly fewer number of steps compared to the more classical routes. Conversion of the terminal alkene to a carboxylic acid followed by benzylic oxidation gives 4,4-disubstituted tetralones. Regioselective Beckmann rearrangement of the corresponding oximes gives 4,4-dialkyl benzazepinones, which serve as intermediates for the syntheses of highly valuable 3,3-dialkylated oxindoles. Use of such oxindoles for the syntheses of pyrrolidinoindolines is illustrated. Finally it should be noted that the chemistry outlined in Scheme 3 should be compatible with a MeO-susbstituent on the aromatic ring, and if so, specific targets such as (−)-esermethole could be prepared more directly starting with the HV-product **11** (Scheme 1) in ~ less than 10 steps from commercially available precursors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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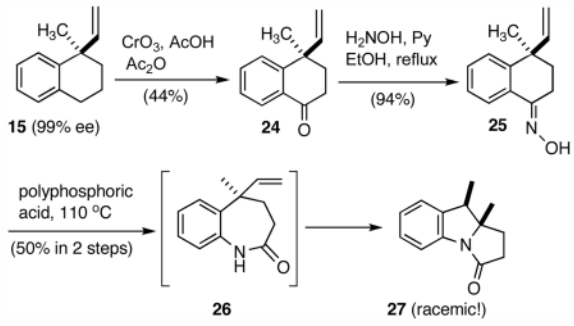
9. See the Supporting Information for the details of the X-ray crystallographic analysis of **21** and **27**. An ORTEP of **21** and **27** with more legible atom-numbering is also included there.

10. Initially we resorted to the Beckmann rearrangement of the oxime **25**, which was readily prepared from the hydrovinylation product **15** in two steps. Beckmann rearrangement of the δ-alkenyloxime **26** did not lead to the expected product **27**; it presumably underwent a deep-seated rearrangement to give a benzopyrrolizidine **28** in *racemic* form as determined by X-ray crystallography (space group P2(1)/n). See Supporting Information for details of the crystallographic analysis and a possible mechanism for the formation of this *racemic* product from a nearly *enantio-pure* starting material.Attempted Beckmann Rearrangement of a δ-Alkenyloxime:



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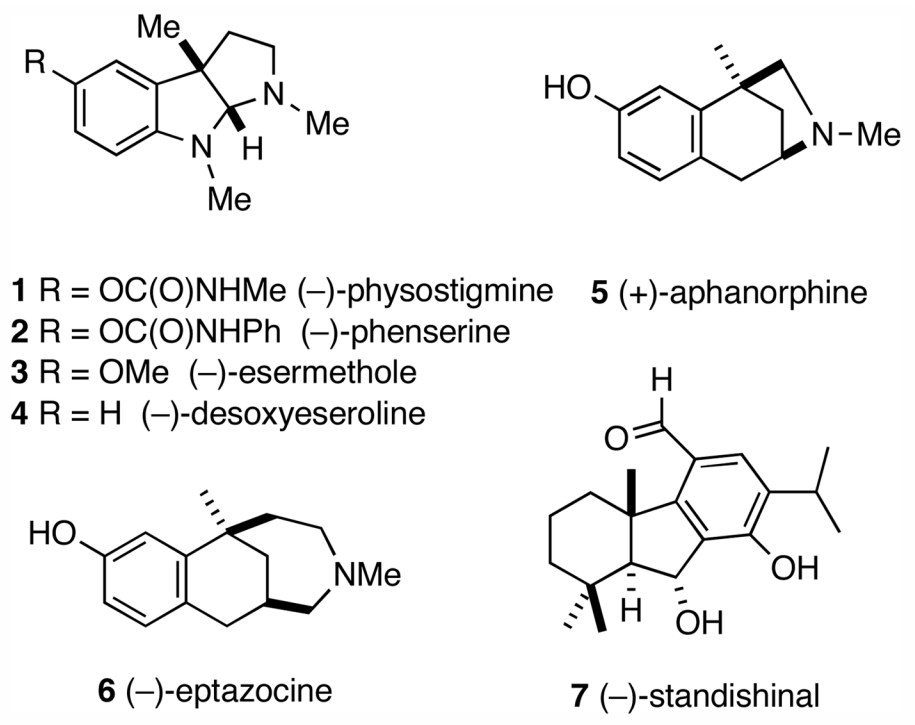


Figure 1.
Medicinally Important Molecules Containing an All-Carbon Benzylic Quaternary Center

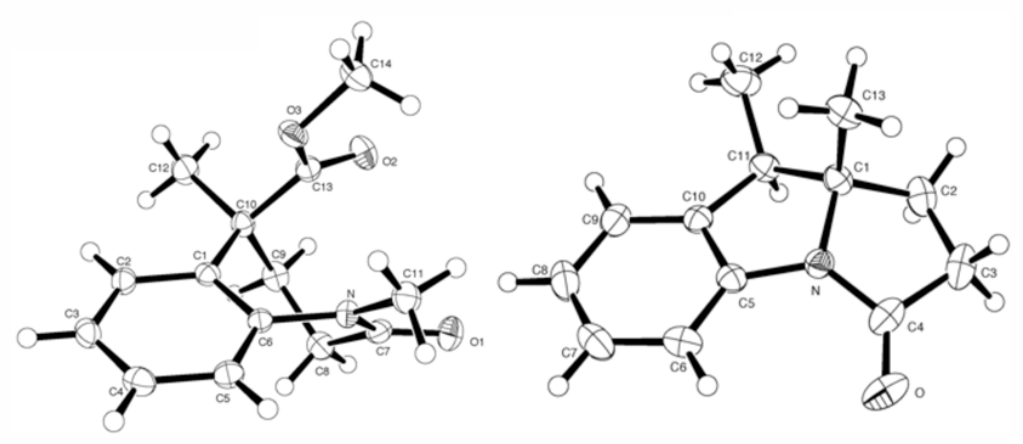
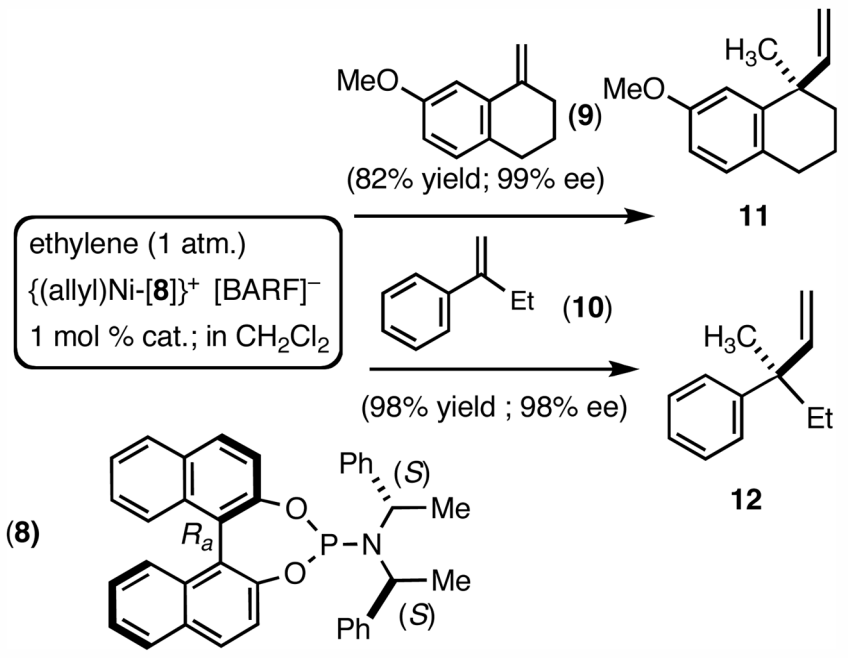
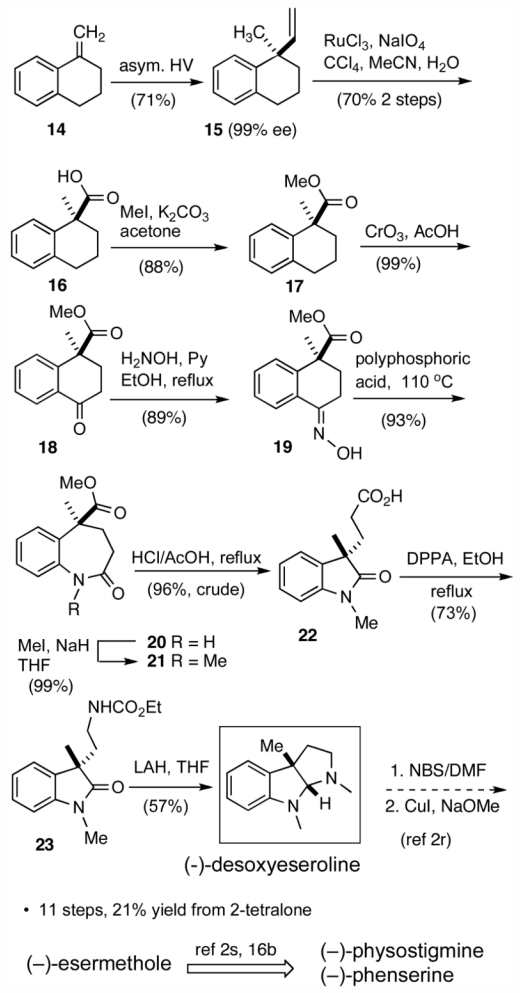


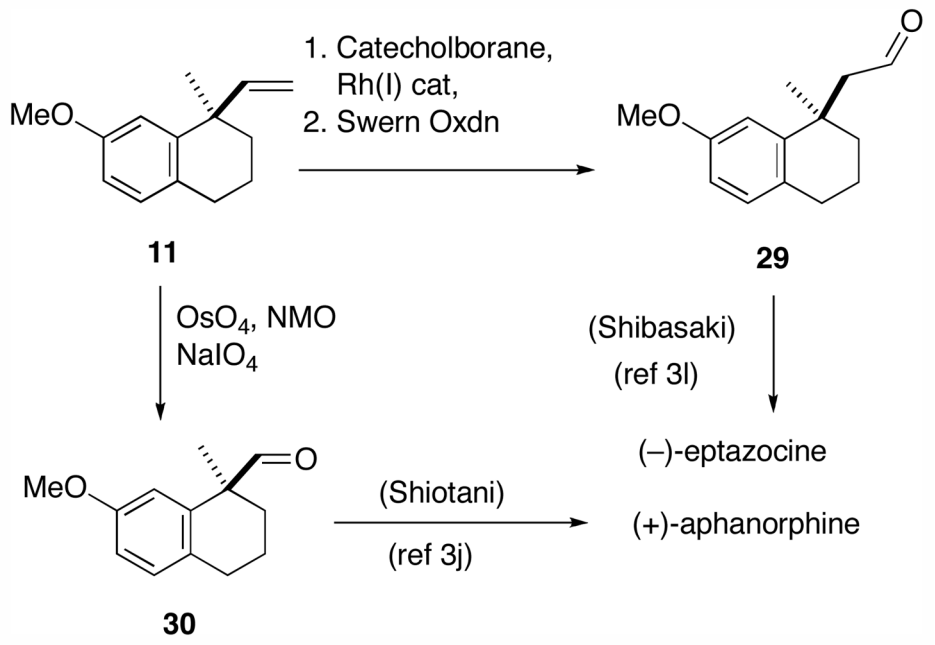
Figure 2.
Solid-State Structures of **21** and **27**[10]



Scheme 1.
All Carbon Quaternary Centers via Catalytic Asymmetric Hydrovinylation



Scheme 2.
Synthesis of Pyrrolidinoindolines via Asymmetric Hydrovinylation



Scheme 3.
Synthesis of Benzomorphans from Products of Asymmetric Hydrovinylation