A Nomination for the Presidential Green Chemistry Challenge Awards Program-2012

Ethylene: A Feedstock for Fine Chemical Synthesis

Primary Sponsor

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- National Science Foundation
- National Institute of Health, General Medical Sciences
- The Ohio State University

Ethylene: A Feedstock for Fine Chemical Synthesis

- With the publication of 17 papers in the area since 2007, several key milestones were celebrated in the past 4 years. In 2010-2011 we published 5 papers in this area. During this period we achieved the following results:

(i) We developed ligands and protocols for the most practical and selective versions of the asymmetric hydrovinylation reaction, and completed the best syntheses of enantiomerically pure non-steroidal anti-inflammatory drugs (NSAID) including both enantiomers of ibuprofen, naproxen, fenoprofen and flurbiprofen, starting with simple styrene derivatives and ethylene in highly catalytic reactions. The starting styrenes themselves were prepared from the arylbromides in a low-pressure vinylation using ethylene.

(b) We demonstrated broad applicability of this chemistry (asymmetric hydrovinylation) in organic synthesis by expansion of viable substrates (e. g., cyclic and acyclic 1,3-dienes, alkenes giving all-carbon quaternary centers, strained bicyclic and small ring-alkenes) and through the enantioselective syntheses of several medicinally relevant compounds.

- The nominated technology is proposed to be considered for an academic award.
- Scope of the nominated technology spans two interrelated focus areas: (1) alternate synthetic (catalytic) pathways for green chemistry; (2) use of alternate reaction conditions
- This research was supported by NSF and NIH, and the Ohio State University.

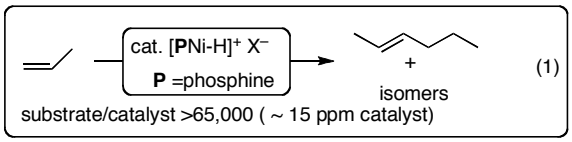
Technical Abstract

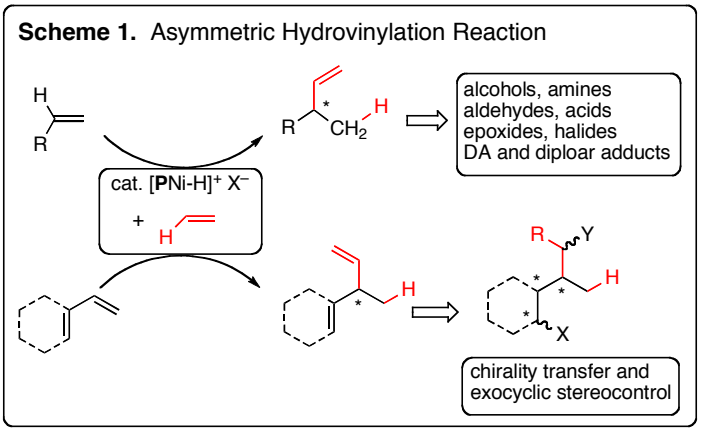
Significant advances in organic synthesis have relied upon the development of new carbon-carbon bond-forming processes that offer clear advantages over traditional methods of accomplishing this important bond construction. Practical methods for *enantioselective* carbon-carbon bond-forming reactions, which use feedstock carbon sources as starting materials, are rare. Development of such a new reaction must meet the following stringent criteria to be qualified as 'green': (i) use of abundantly available, neutral carbon sources; (ii) installation of a functional moiety that can be transformed into other common organic functional groups; (iii) highly catalytic reactions that leave little or no waste including toxic metal residues; (iv) high selectivity, that is reagent-dependent, so that any chosen isomer, including specific enantiomers can be produced; (v) ambient conditions; (vi) ease of recovery of products. Thus, a broadly applicable reaction using ethylene as a reagent for the enantioselective installation of the highly versatile vinyl group could have significant impact in organic synthesis. We have developed new, highly catalytic (substrate:catalyst ratio up to 7412) protocols for nearly quantitative (isolated yields up to >99%) and highly selective (~100% regioselectivity, > 99:1 enantiomeric ratio) codimerization of ethylene and various functionalized vinylarenes, 1,3-dienes and strained alkenes. These reactions proceed under exceedingly mild conditions (-52 ºC to 25 ºC, 1 atmosphere of ethylene) and produce valuable intermediates. This reaction consumes both starting materials and leaves *no* side products, an essential criterion for an eco-friendly process. Highly enantioselective syntheses of the widely used NSAIDs such as ibuprofen, naproxen, flurbiprofen and fenoprofen from the corresponding styrenes and ethylene will be highlighted.

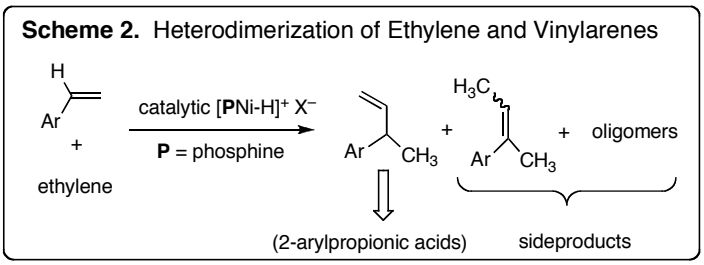
Cyclic and acyclic 1,3-dienes also undergo efficient enantioselective addition of ethylene. Yields up to 99% can be realized for several 1-vinylcycloalkenes and 1-substituted 1,3-butadienes. These discoveries open an expeditious route to several biologically relevant classes

of compounds including bisabolanes, herbindoles and trikentrins, steroid-D-ring 20(*S*) or 20(*R*)-derivatives, (-)-desoxyeseroline, pseudopterosin A-F, G-J and K, L-aglycones and helioporins. Compared to traditional methods, fewer steps are needed for their syntheses, and, since the selectivities are reagent-based, uncommon configurational isomers of these compounds are now easily accessible via this route.

Introduction. The astonishingly high turnover frequency (>625,000 [propylene][Ni]$^{-1}$[h]$^{-1}$) observed for the Ni(phosphine)(allyl)X-catalyzed homodimerization of propene makes this system the most active homogeneous catalyst known.[1] Applications of this chemistry in fine chemical synthesis would be especially attractive if the reaction can be extended to hetero-dimerizations (i.e., dimerization of two different and preferably functionalized olefins) and sufficient selectivity can be achieved. Among these reactions, codimerization of ethylene and other alkenes (hydrovinylation, Scheme 1) would have the highest impact since the vinyl group in the product can be transformed into a large number of useful functional groups. An important application is in the asymmetric hydrovinylation (HV) of vinylarenes (R = Ar in Scheme 1). The resulting HV products, 3-arylbutenes can be readily transformed into widely used non-steroidal anti-inflammatory 2-arylpropionic acids, best exemplified by (*S*)-ibuprofen and (*S*)-naproxen. When applied to 1,3-dienes, the reaction would offer a conceptually new way of addressing other important stereochemical issues including the classic exocyclic stereocontrol problem.[2]



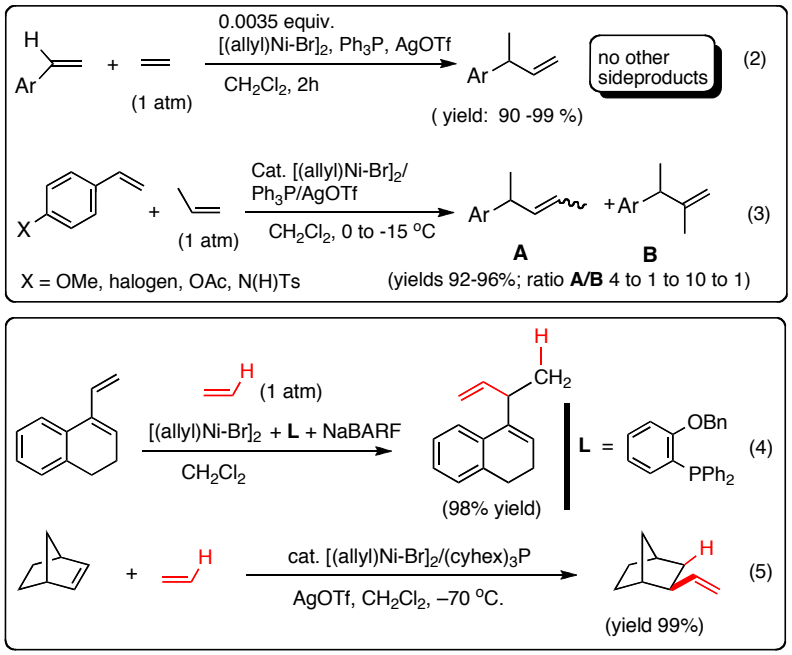




Even though the hydrovinylation reaction (especially that of styrene) has had a long history dating back to 1965, a careful examination[3] of the published work before our initial publications[4] revealed that no catalyst system gave satisfactory yield and selectivity to be of practical value. Most often the reaction was complicated by isomerization of the primary products, and oligomerization of the vinylarene and ethylene (Scheme 2). Besides, the use of high pressures of ethylene and metal components incompatible with sensitive organic groups often limited the utility of many of the procedures reported earlier. *The development of this reaction, its extensions and applications of the intermediates derived through various asymmetric hydrovinylation reactions form the basis of this submission.*

A. A New Protocol for the Heterodimerization of Ethylene/Propylene with Vinylarenes, 1,3-Dienes, and Norbornene. After an extensive scouting program, including mechanistic

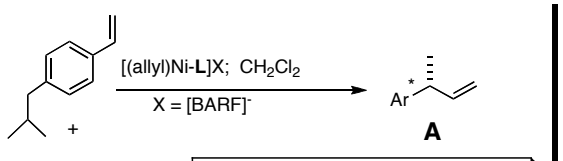
studies, in which we systematically examined the effects of the ligands and the counter ions under a variety of reaction conditions, a new protocol was arrived at. We found that the hydrovinylation of various vinylarenes proceeded with *unprecedented chemical yield and selectivity* when a combination of allylnickel bromide dimer, a weakly coordinating counter ion (e.g., OTf^-) and a tertiary monophosphine (0.07 equiv. Ni) was employed as the precatalyst (Eq. 2). Under these conditions no isomerization of the primary product or oligomerization of either the vinylarene or ethylene was detected. *In sharp contrast to the previously reported Lewis acid-mediated reactions*,[3b] vinylarenes with Lewis basic centers such as ester/ether/carbonyl oxygen or amide nitrogen pose no problems. Many vinylarene precursors for important antiinflammatory 2-arylpropionic acids (naproxen, ibuprofen, fenoprofen, flurbi-profen and ketoprofen) gave excellent yields of the expected hydrovinylation products with ethylene (Eq. 2) and propylene (Eq. 3).



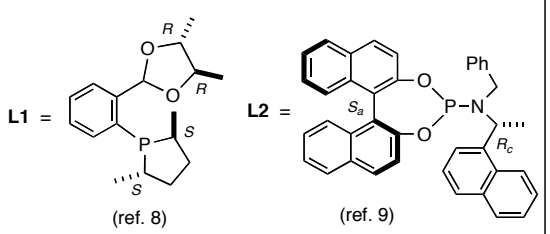
Improvements of reaction conditions and discovery of new ligands have enabled us to carry out highly efficient hydrovinylations of 1,3-dienes[5] and strained alkenes[6] such as norbornenes and cyclobutenes, prototypical examples of which are shown in Eq. 4 and 5.

Catalytic Asymmetric Hydrovinylation Reactions: Synthesis of (*S*)-Ibuprofen, (*S*)-Naproxen and Other 2-Arylpropionic Acids. There are about 16 2-arylpropionic acids currently known, and by and large, the biological activity of these compounds is confined to one of the enantiomers.[7] They are also the most commonly used pharmacologic agents worldwide, with annual worldwide sales estimated to exceed $20 billion,[7b] or greater than 3% of total worldwide pharmaceutical sales. Naproxen (the active ingredient in the over-the-counter painkiller Aleve®) and ibuprofen are two of the most well-known among these drugs. *Catalytic asymmetric hydrovinylation opens a new 'green' route* to this important class of compounds.

Scheme 3. Asymmetric Catalytic Route to an (*S*)-Ibuprofen Intermediate



ligand	S/C	yield (%)	%ee
L1	>1200	99	91
L2	7142	97	96



From our initial synthetic and mechanistic studies using a number of bi- and monodentate phosphines and various counter ions,[4] we discovered a beneficial synergistic interaction between a hemilabile monophosphine ligand and a highly dissociated counter-anion, a concept that has since been found to be broadly applicable. We have since found that two classes of ligands,[8,9] which incorporate this feature, are exceptionally good for Ni-catalyzed asymmetric hydrovinylation reactions including those of vinylarenes. These are illustrated for the synthesis of an intermediate for (*S*)-ibuprofen in Scheme 3.

Several C_2-symmetric *P*-(2-X-aryl)-2,5-dialkylphospholanes[8] (X = dioxolan-2-yl or dioxan-2-yl) [Scheme 3, **L1**], and phosphoramidite ligands[9] [Scheme 3, **L2**], patterned after Feringa's ligands, are highly effective for the Ni(II)-catalyzed asymmetric hydrovinylation of styrenes. Excellent yields (>97%), selectivities for the desired 3-arylbutenes (>99%), high S/C ratios (up to 7142 for **L2**) and ee's (up to 96 %) have been demonstrated in the asymmetric HV of 4-isobutylstyrene (Scheme 3).[9] The resulting 3-arylbutene **A** is readily converted into (*S*)-ibuprofen in a two-step sequence that involves ozonolysis and oxidation.[9b] Sodium salt of ibuprofen can be recrystallized to near optical purity (~100% ee).[10] We have also prepared the starting 4-isobutylstyrene by an ecologically superior route, using Heck reaction of an aryl halide with **ethylene**. This paper appeared in a *Tetrahedron Symposium-in-Print* dealing with Green Chemistry.[11]

Scheme 4. 2-Arylpropionic Acids from 3-Arylbutenes. (*S*)-Ibuprofen

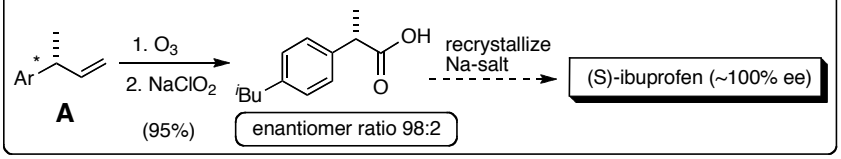
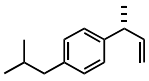
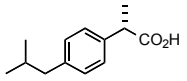
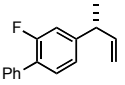
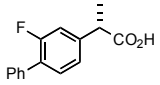
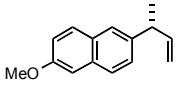
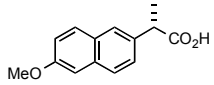
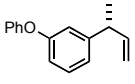
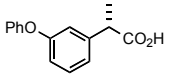


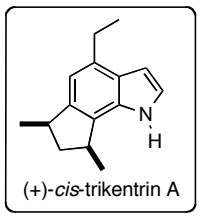
Table 1 summarizes the results of hydrovinylations of vinylarenes using ligand **L2** (Scheme 3)[9b] and the subsequent oxidation of the HV products for the synthesis of the most widely used NSAID 2-arylpropionic acids.

Table 1. Asymmetric Hydrovinylation of Vinylarenes and Synthesis of NSAID Drugs[a]

	Asymmetric Hydrovinylation		Oxidative Degradation to Acid	
Entry	HV Product /yield (%)	ee (%)/conf.	Yield from HV Product	Product (% ee)
1.	 (97)	96, *R*	93	 (*S*)-ibuprofen (96)
2.	 (97)	>97, *R*	95	 (*S*)-flurbiprofen (97)
3.	 (98)	99, *R*	67	 (*S*)-naproxen (99)
4.	 (98)	>97, *R*	91	 (*S*)-fenoprofen (97)

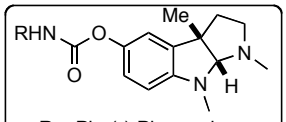
[a] Asymmetric HV using ligand **L2**; See Schemes 3 and 4 and references 9a and 9b.

Comparison to the best existing methods. Currently naproxen, the only drug in this class that is sold as a single enantiomer, is produced via a classical multistep resolution procedure, which is necessarily labor and energy intensive. The best asymmetric catalytic approach to (*S*)-ibuprofen to-date is a ruthenium-catalyzed hydrogenation of a β-arylacrylate,[12a] which proceeds in 97% ee (8 h, 1400 psi H_2, Ru(II)-H_8-BINAP catalyst, S/C 200). However, the low turnover frequency (25 h^{-1}) of the hydrogenation and the circuitous synthesis of the starting acrylate[12b] should make the hydrovinylation method (approximate TOF >3000 h^{-1}; S/C 7142 demonstrated[9]) arguably the best approach for a large-scale synthesis of (*S*)-ibuprofen. No *practical* syntheses of other enantio-pure NSAIDs have been described in the literature.



(+)-*cis*-trikentrin A

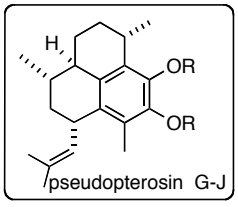
C. Other Hydrovinylation Reactions. Table 2 illustrates the full scope of the asymmetric hydrovinylation reaction. The reaction is remarkably tolerant to various functional groups including an indole nitrogen (entry 2). We have completed an enantioselective synthesis of (+)-*cis*-trikentrin using the HV of product in entry 2.[13]



R = Ph: (-)-Phenserine
R = Me: (-) Physostigmine

All Carbon Quaternary Centers via Catalytic Asymmetric Hydrovinylation.[14] 1-Alkylstyrenes undergo efficient hydrovinylation in the presence of 1 mol% of a Ni(II)-(phosphoramidite)-catalyst. Compound shown in entry 5 (column 3), synthesized in 2 steps from 1-tetralone, took in 11 steps in a previous report![15] We just published the synthesis of medicinally important pyrrolidinoindolines and other molecules using this chemistry.[16]

Exocyclic Stereocontrol. An exocyclic chiral secondary center and presence of asymmetric carbons on the ring to which is attached the chain are an important structural motifs in many biologically relevant molecules such as steroids, pseudopterosins and serrulatanes.[2] A general solution to this classical problem ('the steroid side-chain problem'), is illustrated in entries 7 and 8. In each case, the exocyclic stereogenic center can be installed by an asymmetric hydrovinylation of the 1,3-diene shown. The configuration of the newly created center is controlled by the Ni(II)(phosphoramidite) catalyst, and is independent of the nature of the substrate. Using such control elements, we have completed a total synthesis of pseudopterosin A-F and G-J aglycones by using back-to-back asymmetric HV reactions of a vinylarene, a diene and a tetrahydro-1-*H*-phenalene to set up *all* stereocenters of this complex molecule.[17]

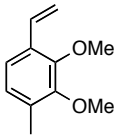
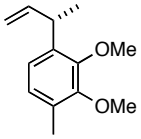
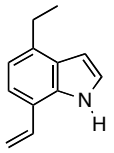
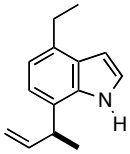
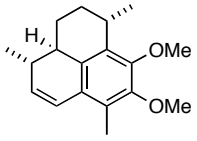
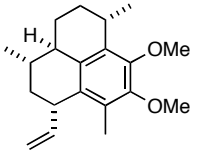
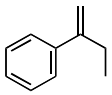
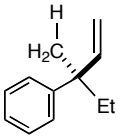
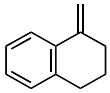
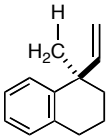
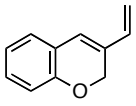
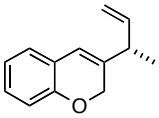
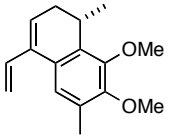
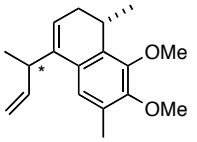
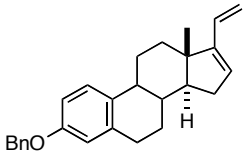
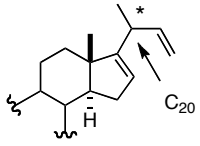
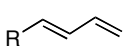
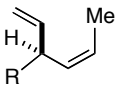
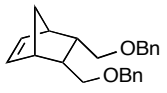
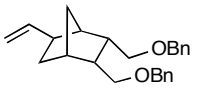


pseudopterosin G-J

A Stereoselective Route to either Steroid-C20(*S*) or -C20(*R*) Derivatives.[18] Using finely tuned phosphoramidite ligands (entry 8) it is possible to synthesize either the C_{20} (*R*)- or the C_{20} (*S*)-steroid derivatives from the corresponding dienes via HV reactions. The HV strategy replaces the current, tedious multi-step routes to these compounds.

Summary. The heterodimerization of olefins is one of a handful of asymmetric reactions that uses a feedstock carbon source for the synthesis of potentially valuable fine chemical intermediates. We have demonstrated its use for the synthesis of popular profen drugs, and other molecules with chiral benzyl centers including all-carbon quaternary centers. With the discovery of a number of different 'tunable' ligands, and of new control elements (e. g., hemi labile ligands and counter-ion effects), the prospects of developing *practical* enantioselective versions of

Table 2. Scope and Utility of Asymmetric Hydrovinylation

entry	substrate	product	yield (%)/ee (%)	comments/ref.
ASYMMETRIC HYDROVINYLATION OF HIGHLY FUNCTIONALIZED VINYLARENES				
1			99/99	precursor for pseudopterosins and helioporins[17]
2.			99/98	tolerates indole-*N*; intermediate for synthesis of trikentrins[13]
3.			99/>99	penultimate intermediate in pseudopterosin synthesis[17]
ALL-CARBON QUATERNARY CENTERS VIA ASYMMETRIC HV				
4.			97/97	asymmetric all-carbon quaternary center[14]
5.			72/99 (previous best synthesis of this molecule: 11 steps![15])	asymmetric all-carbon quaternary center; Intermediate in synthesis of (–)-phenserine [14, 16]
ASYMMETRIC HYDROVINYLATION OF 1,3-DIENES				
6.			99/98	example of exocyclic stereocontrol[5]
7.			92/88 (* = *S*) >90/94 (* = *R*)	example of exocyclic stereocontrol by choice of ligands; intermediate in pseudopterosin synthesis[17]
8.			64/>99 (* = *S*) 59/>99 (* = *R*)	example of exocyclic stereocontrol by choice of ligands; controlling C20 of steroid side-chain.[18]
9.			>90/90-99	Co(II)(DIOP)-catalyzed HV of acyclic dienes-acyclic stereoselection[19]
ASYMMETRIC HYDROVINYLATION OF STRAINED ALKENES				
10.			90/>95	highest ee recorded for bicyclo[2.2.1]alkenes in any C-C bond forming reactions[6b]

other heterodimerization reactions are imminent. One of the most exciting aspects of this reaction is the possibility of *absolute control* of side-chain stereochemistry in cyclic compounds. The most recent entry into this class of reactions is a Co(II)-catalyzed asymmetric hydrovinylation of unactivated linear 1,3-dienes (entry 9 in Table 2).[19]

Relevance to Green Chemistry

- use of ethylene as a carbon source to prepare useful pharmaceutical intermediates
- very high catalytic turnover and the attendant efficiency of the process
- many reactions done under ambient conditions
- exceptionally high chemo- regio- and enantioselectivity and attendant ease of purification
- use of cheap ligands and a non-toxic metal (nickel) as catalyst components
- ancillary discoveries (e. g., synergistic effects of hemilabile ligands and counter-ions, synthesis and applications of new ligands) with potential applications in other catalytic processes

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