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Published on Web 02/09/2006

Highly Enantioselective Hydrovinylation of α-Alkyl Vinylarenes. An Approach to the Construction of All-Carbon Quaternary Stereocenters

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Since the chiral centers connected with four different carbon atoms, all-carbon quaternary stereocenters, were frequently found as the core structure of various biologically active compounds, the development of efficient protocols for enantioselective construction of all-carbon quaternary stereocenters has been a very challenging and active area in organic synthesis nowadays.[1] Although much effort has been devoted to this field, at present, only a few asymmetric carbon−carbon bond-forming reactions were shown to be useful for constructing all-carbon quaternary stereocenters.[2] Moreover, even in the most developed of these methods, such as asymmetric Diels−Alder reactions, coupling reactions of allylmetal intermediates, and intramolecular Heck reactions, the scope and many other problems remain unsolved.[1d] Thus, the search for new efficient methodology, especially a catalytic asymmetric method, is one of the current focuses of research in the enantioselective construction of organic molecules with chiral all-carbon quaternary centers.

The transition-metal-catalyzed hydrovinylation is one of a few practically useful carbon−carbon bond-forming reactions utilizing feedstock carbon sources for the synthesis of high-valuable fine chemicals. The asymmetric hydrovinylation has many potential applications in the synthesis of pharmacologically important compounds, such as Ibuprofen and Naproxen, etc., and has recently attracted much attention.[3] Particularly noteworthy, in the Ni-catalyzed asymmetric hydrovinylation of styrenes, efficient catalysts have been developed by Wilke,[4] RajanBabu,[5] and Leitner[6] using azaphospholane **1**, carbohydrate-derivatized phosphinite **2**, phosphoramidite **3**, and other ligands. With these catalyst systems, the hydrovinylations of styrenes proceeded rapidly, producing 3-aryl-1-butenes in high turnover numbers and high enantioselectivities (up to 95% ee) (Scheme 1). However, despite impressive progress that has been achieved in the asymmetric hydrovinylation of styrene and its derivatives, the asymmetric hydrovinylation of α-alkyl vinylarenes, which has a potential for being a novel methodology for the construction of chiral all-carbon quaternary centers, has not been documented to date.[7] Recently, we reported a palladium-catalyzed asymmetric hydrovinylation of styrenes using chiral spiro phosphoramidites and phosphites as ligands.[8] As a part of our continuing efforts in this area, we herein describe the first highly enantioselective hydrovinylation of α-alkyl vinylarenes using chiral spiro phosphoramidite ligands, which provides a new efficient access to the construction of chiral all-carbon quaternary centers.

Initially, the enantioselective addition of ethylene to α-isopropyl styrene (**9a**) was carried out in CH_2Cl_2 under 1 atm of ethylene at room temperature to evaluate chiral ligands. The data in Table 1 showed that the phosphoramidite **3**, which was previously proven to be highly enantioselective in the hydrovinylation of styrene,[6] was effective in the reaction of α-isopropyl styrene to produce 3,4-dimethyl-3-phenyl-1-pentene (**10a**) in good enantiomeric excess values, but with low conversions (entries 1 and 2). We then tested the chiral spiro monophosphorus ligands **4**−**8** (Figure 1), which

Scheme 1

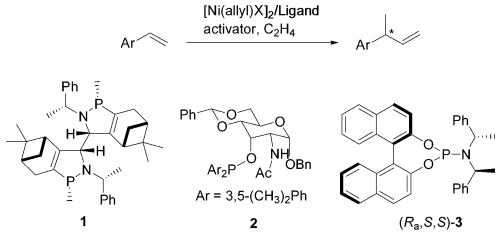
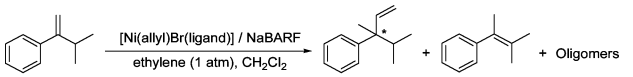


Table 1. Asymmetric Hydrovinylation of α-Isopropyl Styrene[a]



entry	ligand	temp (°C)/ time (h)	conv. (%)[b]	Selectivity (%)[c] 10a	11a	oligomer[d]	% ee of **10a**[e]
1	(*S*$_a$,*S*,*S*)-**3**	rt/6.5	67	87	5	8	88 (*R*)
2	(*S*$_a$,*R*,*R*)-**3**	rt/6.5	30	85	13	2	83 (*R*)
3	(*R*)-**4**	rt/5.0	100	66	13	21	44 (*R*)
4	(*R*)-**5**	rt/5.0	100	64	16	20	75 (*R*)
5	(*R*)-**6**	rt/6.5	73	26	19	55	53 (*R*)
6	(*R*)-**7a**	rt/5.0	98	66	24	11	72 (*R*)
7	(*R*)-**7b**	rt/9.0	89	66	23	11	77 (*R*)
8	(*R*)-**7c**	rt/9.0	78	74	18	8	71 (*R*)
9	(*S*$_a$,*R*,*R*)-**8**	rt/6.5	96	82	2	16	99 (*S*)
10[f]	(*S*$_a$,*R*,*R*)-**8**	rt/9.0	92	85	3	12	99 (*S*)
11	(*R*$_a$,*R*,*R*)-**8**	rt/5.0	16	45	trace	55	94 (*R*)
12	(*S*$_a$,*R*,*R*)-**8**	10/8.5	63	97	3	trace	98 (*S*)
13	(*S*$_a$,*R*,*R*)-**8**	0/8.5	63	96	4	trace	98 (*S*)
14	(*S*$_a$,*R*,*R*)-**8**	35/2.5	96	84	3	13	99 (*S*)

[a] Conditions: [Ni(allyl)Br(ligand)]/NaBARF/**9a** = 0.02/0.021/0.2 (mmol), $M_{[sub]}$ = 0.05 M, rt = 20−25 °C. [b] Determined by GC. [c] On the basis of the converted substrate, determined by GC. [d] Oligomerization products of **9a** and secondary hydrovinylation products. [e] Determined by chiral GC (Supelco β-DEX 120, 30 m). Absolute configuration was determined by correlation with known compound. [f] 5 mol % of catalyst was used.

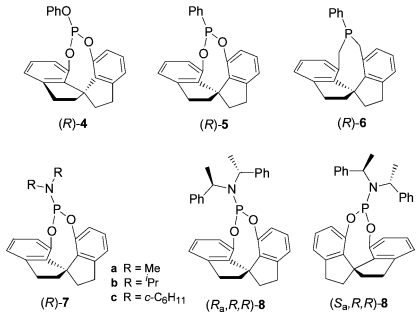
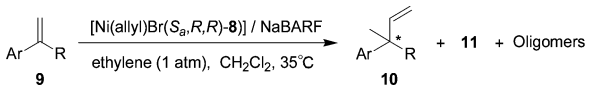


Figure 1. Chiral spiro monophosphorus ligands.

were recently developed in our laboratory and have been demonstrated to be highly enantioselective in the asymmetric hydrogenation[9] and other asymmetric reactions.[10] Ligands **4**−**7** were found to be efficient for the asymmetric hydrovinylation of α-isopropyl

10.1021/ja057654y CCC: $33.50

Table 2. Enantioselective Hydrovinylation of α-Alkyl Vinylarenes Catalyzed by [Ni(allyl)Br(S_a,*R*,*R*)-**8**][a]



entry	Substrate (**9**) Ar	R	crude yield (%)[b]	selectivity of **10** (%)	ee of **10** (%)[c]
1	Ph	*i*-Pr	89	84 (**10a**)	99 (*S*)
2	*p*-MePh	*i*-Pr	96	89 (**10b**)	97
3	*m*-MePh	*i*-Pr	96	89 (**10c**)	98
4	*m*-MeOPh	*i*-Pr	95	84 (**10d**)	98
5	*p*-MeOPh	*i*-Pr	94	86 (**10e**)	98
6	*p*-ClPh	*i*-Pr	76	85 (**10f**)	94
7	Ph	Et	80	89 (**10g**)	70 (*S*)
8	Ph	*n*-Pr	92	84 (**10h**)	82
9	Ph	*i*-Bu	92	86 (**10i**)	88
10	2-naphthyl	*i*-Pr	94	80 (**10j**)	99
11	2-naphthyl	*c*-C_6H_{11}	92	86 (**10k**)	99

[a] Conditions: see Table 1; T = 35 °C. [b] Purified by a short silica gel column chromatography. Conversions were 95−100%. [c] Determined by chiral GC and HPLC (for details, see Supporting Information).

styrene with good to excellent conversions, but in only moderate chemo- and enantioselectivities (entries 3−8). It was remarkable that the spiro phosphoramidite ligand (S_a,*R*,*R*)-**8** gave the product **10a** in 99% ee with 96% conversion and 82% chemoselectivity (entry 9). In a contrast, the ligand (R_a,*R*,*R*)-**8**, with mismatched chiralities, gave very low conversion and chemoselectivity (entry 11). The superiority of ligand **8** over **7** on the activity and enantioselectivity showed that the interaction of the pheny ring of the ligand with a Ni center in the catalyst might be crucial.[6b] The reaction is sensitive to the temperature. When the reaction was carried out at 10 or 0 °C, the chemoselectivity of product **10a** was improved significantly to 97 and 96%, respectively, with the enantioselectivity remaining at 98%, but the conversion of substrate **9a** was lowered to 63% (entries 12 and 13). As the temperature was increased to 35 °C, the reaction became faster without loss of selectivities (entry 14). In addition to CH_2Cl_2, the hydrovinylation of **9a** could also be performed in 1,2-dichloroethane and toluene, giving desired products in 89 and 97% chemoselectivity and 98% ee, while the conversions were only moderate (53 and 67%, respectively). The reaction was completely prevented if THF and Et_2O and other coordinating solvents were employed. The activator NaBARF (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was found to be vital for obtaining high conversion of substrate. The conversion of **9a** became less than 10% when other activators, such as $AgPF_6$, $AgSbF_6$, $AgBF_4$, $AgClO_4$, and AgOTf, were used.

With optimized reaction conditions, a variety of α-alkyl vinylarenes can be successfully hydrovinylated to form new arene compounds bearing an all-carbon quaternary stereocenter. As illustrated in Table 2, the hydrovinylations of the α-alkyl styrenes without an electron-deficient group at a *para* or *meta* position on phenyl rings gave almost quantitative conversion of substrates (Table 2, entries 1−5). While in the case of α-isopropyl 4-chlorostyrene, the electron-withdrawing chlorine substitution led a low conversion (76% in 15 h). The *ortho*-substituted α-alkylstyrenes, such as α-isopropyl 2-methylstyrene and α-ethyl 2-methylstyrene, were also examined at the same conditions, and no reaction was observed, indicating that the steric hindrance of substrate has a remarkable negative effect on the reactivity. The nature of the substrate has little influence on the chemoselectivity of hydrovinylation products **10**. The chemoselectivities for all investigated α-alkyl vinylarenes were in the range of 80−89%. There was a high correlation between the enantioselectivity of the reaction and the size of α-alkyl group in the substrates **9**. When the ethyl group in substrate **9g** was *n*-Pr (**9h**), *i*-Bu (**9i**), and *i*-Pr (**9a**), the enantiomeric excess values of the corresponding hydrovinylation products increased successively from 70 to 82, 88, and 99% (Table 2, entries 1 and 7−9). The substrates with a α-isopropyl and α-cyclohexyl gave excellent enantioselectivities (94−99% ee), showing that a bulky alkyl group at the α-position of vinylarenes is definitely necessary for obtaining chiral all-carbon quaternary centers in high enantioselectivity in the hydrovinylation reaction.

In summary, we have developed a highly efficient catalyst system for the asymmetric hydrovinylation of α-alkyl vinylarenes by using spiro phosphoramidite ligands, which provided a new approach to construct all-carbon quaternary stereocenters in excellent enantioselectivity. The hydrovinylation products, bearing a chiral all-carbon quaternary center, are potentially useful intermediates in the synthesis of versatile optically enriched molecules, such as chiral carboxylic acids, aldehydes, etc. The scope and the applications of this discovery are being investigated in our laboratory.

Acknowledgment. We thank the National Natural Science Foundation of China, the Major Basic Research Development Program (Grant No. G2000077506), and the Ministry of Education of China for financial support.

Supporting Information Available: Experimental procedures, the characterizations of substrates and products, and the analyses of enantiomeric excess values of hydrovinylation products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA057654Y