Palladium-catalysed Asymmetric Hydroalkenylation of Norbornene

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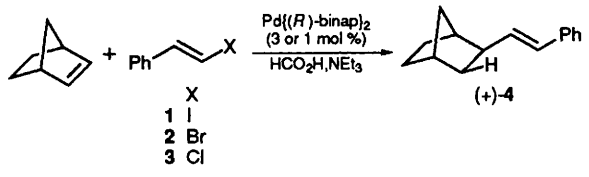
Catalytic asymmetric hydroalkenylation of norbornene (bicyclo[2.2.1]hept-2-ene) can be performed in 93% e.e. using 1-methyl-2-(ethoxycarbonyl)ethenyl triflate **5** as alkenylation agent and Pd{(*R*)-binap}$_2$ as chiral catalyst.

Combination of the Heck type arylation and alkenylation of olefins with palladium-catalysed cross-coupling reactions (so-called three-component coupling reactions) has provided novel synthetic means of organic compounds.[1,2] Hydroalkenylation and hydroarylation of norbornene (bicyclo[2.2.1]hept-2-ene) are simple examples of this type of reactions.[2] Treatment of norbornene with aryl or alkenyl iodide and formic acid as a hydride source in the presence of a palladium catalyst and a base gives 2-aryl- or 2-alkenyl-norbornane, respectively. Despite the synthetic usefulness of the three-component coupling reactions, successful applications of such reactions to catalytic asymmetric synthesis are scarce. Recently, Brunner and Kramler[2a] presented asymmetric hydroarylation of norbornene with aryl iodides to give optically active *exo*-2-arylnorbornanes of up to 38% e.e. We report here the first efficient catalytic systems for asymmetric hydroalkenylation of norbornene where optically active *exo*-2-alkenylnorbornanes of up to 93% e.e. can be obtained.

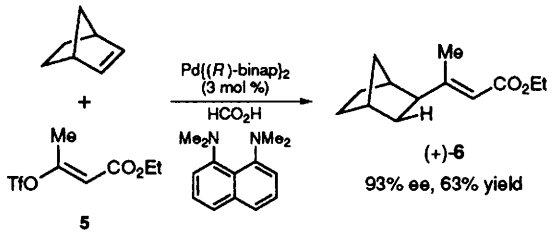


Scheme 1

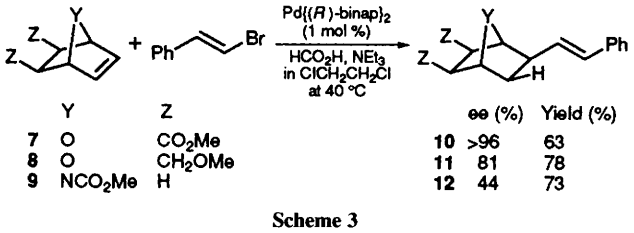
Table 1 Catalytic asymmetric hydroalkenylation of norbornene with *trans*-β-halogenostyrenes and formic acid[a]

Entry	Halogenostyrene	Solvent	*T*/°C[b]	% ee of **4**	Yield of **4** (%)
1	**1** (X = I)	DMF	40	0	91
2	**2** (X = Br)	DMF	40	70	76
3	**2** (X = Br)	$ClCH_2CH_2Cl$	40	84	70
4	**3** (X = Cl)	DMF	60	55	31[c]

[a] Reaction conditions: norbornene (6.0 mmol), styryl halide (3.0 mmol), formic acid (3.0 mmol), NEt_3 (6.0 mmol), Pd{(*R*)-binap}$_2$ [3 mol % (entries 1, 2 and 4) or 1 mol % (entry 3)], solvent (12 ml), under a nitrogen atmosphere. Reaction time (h): 19 (entry 1), 41 (entry 2), 168 (entry 3), 72 (entry 4). [b] Reaction temperature. [c] 45% of **3** was recovered unreacted.



Scheme 2 *Conditions*: 40 °C for 86 h in $ClCH_2CH_2Cl$



Scheme 3

Asymmetric hydroalkenylation of norbornene was examined with *trans*-β-halogenostyrenes (**1–3**) as alkenylation reagents and Pd{(*R*)-binap}$_2$[3] as chiral catalyst (Scheme 1). The enantioselectivity dramatically varied with halogen atoms attached to styryl group (Table 1).

Treatment of norbornene with β-bromostyrene **2** and formic acid in DMF in the presence of triethylamine as the base and the palladium catalyst at 40 °C gave (1*S*,2*S*,4*R*)-(+)-*exo*-2-styrylnorbornane **4** of 70% e.e. in 76% yield (entry 2).‡ The enantioselectivity was improved to 84% e.e. by the use of 1,2-dichloroethane as a low polar solvent in place of DMF (entry 3). In contrast, β-iodostyrene **1** formed racemic **4** (entry 1). *trans*-β-Chlorostyrene **3** exhibited significantly lower reactivity than the bromide and iodide and required an elevated reaction temperature (60 °C) (entry 4). In this case, (+)-**4** of modest enantiomeric purity (55% e.e.) was obtained.

Enantioselective hydroalkenylation of norbornene could be performed also with alkenyl triflate **5** as alkenylation agent (Scheme 2). The reaction performed in 1,2-dichloroethane in the presence of 1,8-bis(dimethylamino)naphthalene (proton sponge) as the base and Pd{(*R*)-binap}$_2$ catalyst at 40 °C gave the alkenylation product (+)-**6** of 93% e.e. in 63% yield.§ Almost the same enantioselectivity (92% e.e.) was gained with a highly basic and sterically demanding 1,2,2,6,6-pentamethylpiperidine in place of proton sponge. On the other hand, more compact triethylamine and a less basic pyridine derivative (2,6-di-*tert*-butyl-4-methylpyridine) provided (+)-**6** of lower enantiomeric purity (75 and 58% e.e., respectively).

The present catalytic system using β-bromostyrene as the alkenylation reagent is also applied to the asymmetric hydroalkenylation of 7-oxanorbornene derivatives (**7** and **8**) and 7-azanorbornene derivative **9** (Scheme 3). Thus the corresponding hydroalkenylation products (**10**, **11**, and **12**, respectively) were obtained in >96–44% e.e. under the same reaction conditions as entry 3 in Table 1.

We found that nature of leaving groups in alkenylation reagents has prominent effects on the enantioselectivity. Thus alkenyl bromide **2** and triflate **5** gave rise to high enantioselectivities (84 and 93% e.e., respectively), while alkenyl iodide **1** formed a racemic product. These findings provide useful information for developing enantioselective three-component coupling reactions. The scope of application of the novel asymmetric reaction is now under investigation.[6]

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Footnotes

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‡ All new compounds prepared in this study were fully characterised

by elemental analysis and NMR and IR spectroscopy. The enantiomeric purity of (+)-**4** was determined by HPLC using a chiral stationary phase column (Sumichiral OA-2000) after converting (+)-**4** into *N*-phenyl-*exo*-2-norbornanecarboxamide. The absolute configuration (1*S*,2*S*,4*R*) was confirmed by converting (+)-**4** into known (+)-*exo*-2-(methoxycarbonyl)norbornane: $[\alpha]_D^{20}$ +20.3 (*c* 0.76, 95% EtOH; 77% e.e.) {(lit.[4] $[\alpha]_D^{26}$ +34.2 (95% EtOH)}.

§ The enantiomeric purity of (+)-**6** was determined by GLC using a chiral capillary column [Chrompack CP-Cyclodextrin-β-2,3,6-M-19 (25 m)]. The absolute configuration was assigned to be (1*S*,2*S*,3*R*) by converting (+)-**6** into known (+)-*exo*-2-acetylnorbornane: $[\alpha]_D^{20}$ +54.6 (*c* 1.06, EtOH; 91% e.e.) {lit.[5] $[\alpha]_D^{23}$ + 60.8 (*c* 0.99, EtOH)}.

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