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Palladium-Catalyzed Asymmetric Alkenylation of Cyclic Olefins

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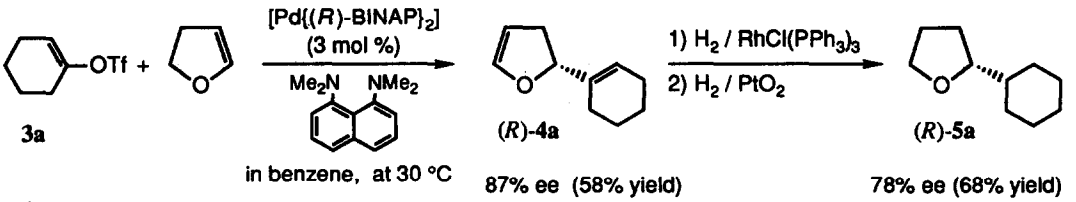
Abstract: The reaction of 2,3-dihydrofuran with alkenyl triflates in benzene or toluene in the presence of 1,8-bis(dimethylamino)naphthalene and a catalytic amount of Pd{(*R*)-BINAP}$_2$ gave optically active 2-alkenyl-2,3-dihydrofurans in high enantioselectivities (>96–87% ee). Under similar reaction conditions, 1-(methoxycarbonyl)-2-pyrroline was alkenylated in >99–96% ee.

Palladium-catalyzed arylation and alkenylation of olefins (Heck reaction) have been widely applied in organic synthesis.[1] We recently found that the catalytic asymmetric arylation of cyclic olefins proceeds in high enantioselectivity in the reaction system using aryl triflates as arylating reagents.[2,3] For example, treatment of 2,3-dihydrofuran with aryl triflates in benzene at 40 °C in the presence of a base and a chiral palladium catalyst, generated in situ from Pd(OAc)$_2$ and (*R*)-BINAP,[4] gave (*R*)-2-aryl-2,3-dihydrofuran (**1**) of over 90% ee and a minor amount of regioisomer (*S*)-2-aryl-2,5-dihydrofuran (**2**) ((*R*)-**1**/(*S*)-**2** ≈ 7/3). This asymmetric catalysis involves a novel kinetic resolution process that efficiently enhances the enantiomeric purity of (*R*)-**1** by selective elimination of (*S*)-arylation product as the minor isomer **2** from the catalytic cycle.[2d] Thus, while the selectivity of enantiofaces of 2,3-dihydrofuran in the arylation reaction ranged between 8/2 and 9/1 under the catalytic conditions, the enantiomeric purity of (*R*)-**1** exceeded 96% ee for a variety of aryl triflates by the kinetic resolution process.

In this paper, we describe an enantioselective alkenylation of cyclic olefins with alkenyl triflates in the presence of a chiral palladium catalyst. The selectivity of enantiofaces of olefin in the alkenylation reactions was found to be much higher than that observed in the arylation systems, and almost enantiomerically pure products were obtained without the kinetic resolution process giving undesirable regioisomer.



Scheme 1

Treatment of 2,3-dihydrofuran (0.30 mL, 4.0 mmol) with 1-cyclohexenyl triflate (**3a**, 236 mg, 1.03 mmol) in benzene (4 mL) at 30 °C for 91 h in the presence of 1,8-bis(dimethylamino)naphthalene (proton sponge, 429 mg, 2.0 mmol) and a catalytic amount of Pd{(*R*)-BINAP}$_2$[5] (40.7 mg, 0.030 mmol) gave (*R*)-2-(1-cyclohexenyl)-2,3-dihydrofuran (**4a**) of 87% ee as the sole alkenylation product (87.7 mg, 58% yield) (Scheme

Table 1. Effect of Base and Solvent on the Asymmetric Alkenylation of 2,3-Dihydrofuran with 2-(Ethoxycarbonyl)-1-cyclohexenyl Triflate (**3b**) Catalyzed by Pd{(*R*)-BINAP}$_2$ [a]

entry	base [b]	solvent	reaction time (h)	product (**4b**) % ee [c]	product (**4b**) yield (%) [d]
1	Et_3N	benzene	72	81	70
2	*i*-Pr_2NEt	benzene	72	65	69
3	proton sponge	benzene	19	93	78
4	proton sponge	toluene	19	94	84 [e]
5	proton sponge	THF	19	78	85
6	proton sponge	$ClCH_2CH_2Cl$	120	56	63 [f]
7	proton sponge	MeCN	96	40	72

[a] The reaction was carried out at 60 °C. Initial conditions: **3b**/2,3-dihydrofuran/base/Pd{(*R*)-BINAP}$_2$ = 1/4/2/0.03. [b] Proton sponge: 1,8-bis(dimethylamino)naphthalene. [c] Determined by ^{1}H NMR using Eu(hfc)$_3$. [d] Determined by GLC using tridecane as an internal reference. [e] Isolated yield. [f] 29% of **3b** was recovered unreacted.

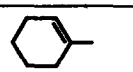
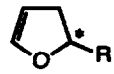
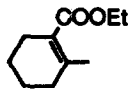
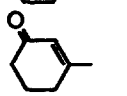
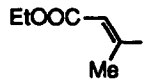
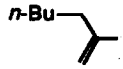
1).[6] As we confirmed previously, the kinetic resolution giving the regioisomer (2,5-dihydrofuran derivative) is caused by acetate anion generated from $Pd(OAc)_2$ as the catalyst precursor.[2d,e] The use of isolated Pd{(*R*)-BINAP}$_2$ catalyst provided the reaction system not containing acetate anion and gave rise to the regioselective formation of **4a**.

Hydrogenation of **4a** gave 2-cyclohexyltetrahydrofuran (**5a**) of 78% ee (Scheme 1). GLC analysis using a chiral capillary column (Chrompack CP-Cyclodextrin-β-2,3,6-M-19, 25 m) revealed that this compound has the same configuration as (*R*)-2-cyclohexyltetrahydrofuran derived from (*R*)-2-phenyl-2,3-dihydrofuran (63% ee)[2a] by hydrogenation in the presence of Wilkinson catalyst and 5% rhodium on alumina catalyst. Hence, the absolute configuration of **4a** was determined to be (*R*).

Table 1 shows the effect of base and solvent on the asymmetric alkenylation of 2,3-dihydrofuran with 2-(ethoxycarbonyl)-1-cyclohexenyl triflate (**3b**) at 60 °C. 1,8-Bis(dimethylamino)naphthalene as a highly basic and sterically demanding amine was found to be the most efficient base for the enantioselective formation of 2-[2-(ethoxycarbonyl)-1-cyclohexenyl]-2,3-dihydrofuran (**4b**) (entries 1–3). The high enantioselectivity around 94% ee was obtained in aromatic solvents such as benzene and toluene (entries 3 and 4). The reaction performed in THF proceeded at a comparable reaction rate to that in aromatic solvents but the enantioselectivity was lower (entry 5). Use of 1,2-dichloroethane and acetonitrile as the solvents retarded the reaction and lowered the enantioselectivity (entries 6 and 7).

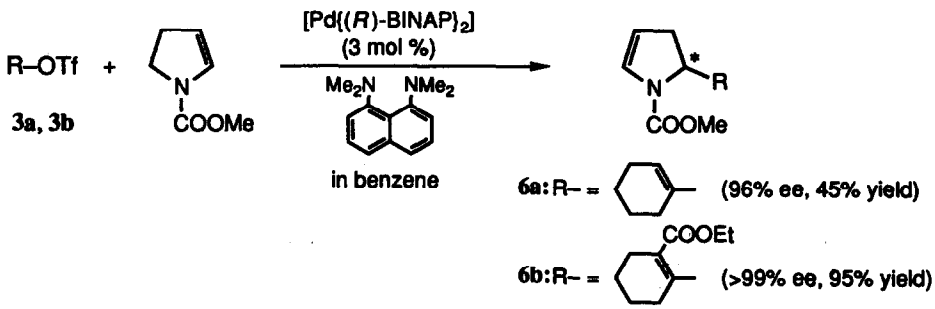
Table 2 summarizes the results of the catalytic reactions of 2,3-dihydrofuran with several alkenyl triflates.[6] Low reaction temperature (30 °C) was required to obtain high enantioselectivity in the reaction of 1-cyclohexenyl triflate (**3a**) (entry 1). On the other hand, the reactions of alkenyl triflates bearing an electron-withdrawing group at the vinyl carbon (**3b**, **3c**, and **3d**) proceeded in extremely high enantioselectivities (>96% ee) even at higher temperatures (entries 2–4). The reaction of 1-pentylethenyl triflate (**3e**) did not proceed at 60 °C (entry 5).

Table 2. Asymmetric Alkenylation of 2,3-Dihydrofuran with Alkenyl Triflates (ROTf) (3) Catalyzed by Pd{(*R*)-BINAP}$_2$ [a]

entry	alkenyl triflate (R)	reaction temp (°C)	reaction time (h)	product	% ee [b]	yield (%) [c]
1	3a 	30	91	4a 	87 (*R*)	58 (74) [d]
2	3b 	40	56	4b	>96 [e]	62
3	3c 	60	20	4c	>96 [e]	50 (67)
4	3d 	60	13	4d	>96 [e]	50 (84)
5	3e 	60	48		no reaction	

[a] The reaction was carried out in benzene using proton sponge as the base. Initial conditions: 3/2,3-dihydrofuran/proton sponge/Pd{(*R*)-BINAP}$_2$ = 1/4/2/0.03. [b] Determined by ^{1}H NMR using Eu(hfc)$_3$. [c] Isolated yield. The values in parentheses are GLC yields. [d] 16% of 3a was recovered unreacted. [e] See ref. 7.

Under the similar reaction conditions, 1-(methoxycarbonyl)-2-pyrroline was alkenylated in high enantioselectivities (Scheme 2).[7,8] Particularly, the reaction with 2-(ethoxycarbonyl)-1-cyclohexenyl triflate (3b) gave enantiomerically pure product (6b) (>99% ee). Here again the selectivity of enantiofaces is much higher than that in the corresponding arylation systems.[2b]



Scheme 2. Initial conditions: 3/2-pyrroline/proton sponge/Pd{(*R*)-BINAP}$_2$ = 1/4/2/0.03. Reaction temperature (°C): 30 (3a), 60 (3b). Reaction time (h): 336 (3a), 20 (3b). The enantiomeric purity was determined by HPLC using a chiral stationary phase column (Sumipax OA-2000).

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6. **[4a]** (87% ee): $[\alpha]_D^{20}$ –79.2 (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.50–1.75 (br, 4 H), 1.95–2.13 (br, 4 H), 2.45 (ddt, *J* = 15.2, 8.9, and 2.3 Hz, 1 H), 2.69 (ddt, *J* = 15.2, 10.9, and 2.3 Hz, 1 H), 4.86 (dd, *J* = 10.9 and 8.9 Hz, 1 H), 4.87 (q, *J* = 2.3 Hz, 1 H), 5.68–5.78 (br, 1 H), 6.32 (q, *J* = 2.3 Hz, 1 H). HRMS (EI): calcd for $C_{10}H_{14}O$, 150.1045; found, 150.1052. **[4b]** (>96% ee): $[\alpha]_D^{20}$ +58.6 (*c* 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.29 (t, *J* = 7.3 Hz, 3 H), 1.53–1.72 (br, 4 H), 2.10–2.48 (br, 4H), 2.37 (ddt, *J* = 15.5, 8.9, and 2.3 Hz, 1 H), 2.98 (ddt, *J* = 15.5, 11.2, and 2.3 Hz, 1 H), 4.18 (q, *J* = 7.3 Hz, 2 H), 4.89 (q, *J* = 2.3 Hz, 1 H), 5.76 (dd, *J* = 11.2 and 8.9 Hz, 1 H), 6.31 (q, *J* = 2.3 Hz, 1 H). IR (KBr): 1708 cm^{-1}. HRMS (EI): calcd for $C_{13}H_{18}O_3$, 222.1256; found, 222.1273. **[4c]** (>96% ee): $[\alpha]_D^{20}$ –43.3 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.04 (qui, *J* = 6.3 Hz, 2 H), 2.33 (q, *J* = 6.3 Hz, 2 H), 2.41 (t, *J* = 6.3 Hz, 2 H), 2.47 (ddt, *J* = 15.2, 8.6, and 2.3 Hz, 1 H), 2.93 (ddt, *J* = 15.2, 10.9, and 2.3 Hz, 1 H), 4.93 (q, *J* = 2.3 Hz, 1 H), 5.03 (dd, *J* = 10.9 and 8.6 Hz, 1H), 6.05 (s, 1 H), 6.35 (q, *J* = 2.3 Hz, 1 H). IR (KBr): 1672 cm^{-1}. HRMS (EI): calcd for $C_{10}H_{12}O_2$, 164.0837; found, 164.0822. **[4d]** (>96% ee): $[\alpha]_D^{20}$ +100.0 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.28 (t, *J* = 7.3 Hz, 3 H), 1.92 (d, *J* = 1.3 Hz, 3 H), 2.32 (ddt, *J* = 15.5, 8.6, and 2.3 Hz, 1 H), 3.10 (ddt, *J* = 15.5, 11.2, and 2.3 Hz, 1 H), 4.14 (q, *J* = 7.3 Hz, 2 H), 4.92 (q, *J* = 2.3 Hz, 1 H), 5.67 (q, *J* = 1.3 Hz, 1 H), 6.19 (dd, *J* = 11.2 and 8.6 Hz, 1 H), 6.33 (q, *J* = 2.3 Hz, 1 H). IR (KBr): 1712 cm^{-1}. HRMS (EI): calcd for $C_{10}H_{14}O_3$, 182.0943; found, 182.0960.
7. Although absolute configurations of **4b–4d**, **6a**, and **6b** were not determined, (*R*) configuration is reasonable based on the reaction mechanism. See ref. 2d.
8. Compounds **6a** and **6b** are mixtures of the two rotamers about the N–COOMe bond, respectively. At the NMR time-scale (^1H, 270 MHz), the rotamers are in a rapid equilibrium at room temperature but are observed as independent species below –20 °C. **[6a]** (96% ee): $[\alpha]_D^{20}$ +130.3 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, –20 °C, 1.6 : 1 mixture of the rotamers): (major isomer) δ 1.45–1.70 (br, 4 H), 1.82–2.10 (br, 4 H), 2.26–2.42 (m, 1 H), 2.86–3.04 (m, 1 H), 3.73 (s, 3 H), 4.56 (dd, *J* = 11.2 and 4.3 Hz, 1 H), 4.98 (dt, *J* = 4.3 and 2.3 Hz, 1 H), 5.57 (br, 1 H), 6.53 (dt, *J* = 4.3 and 2.3 Hz, 1 H); (minor isomer) δ 1.45–1.70 (br, 4 H), 1.82–2.10 (br, 4 H), 2.26–2.42 (m, 1 H), 2.86–3.04 (m, 1 H), 3.70 (s, 3 H), 4.46 (dd, *J* = 11.2 and 4.3 Hz, 1 H), 5.02 (dt, *J* = 4.3 and 2.3 Hz, 1 H), 5.47 (br, 1 H), 6.67 (dt, *J* = 4.3 and 2.3 Hz, 1 H). IR (KBr): 1714 cm^{-1}. HRMS (EI): calcd for $C_{12}H_{17}NO_2$, 207.1259; found, 207.1243. **[6b]** (>99% ee): $[\alpha]_D^{20}$ +147.5 (*c* 1.7, $CHCl_3$). ^1H NMR ($CDCl_3$, –40 °C, 1.2 : 1 mixture of the rotamers): (major isomer) δ 1.31 (t, *J* = 7.3 Hz, 3 H), 1.49–1.61 (br, 2 H), 1.62–1.78 (br, 2 H), 1.98–2.18 (br, 3 H), 2.24–2.42 (m, 1 H), 2.46–2.62 (br, 1 H), 3.16–3.32 (m, 1 H), 3.73 (s, 3 H), 4.16 (q, *J* = 7.3 Hz, 2 H), 5.05 (dt, *J* = 4.3 and 2.3 Hz, 1 H), 5.61 (dd, *J* = 11.6 and 5.6 Hz, 1 H), 6.53 (dt, *J* = 4.3 and 2.3 Hz, 1 H); (minor isomer) δ 1.34 (t, *J* = 7.3 Hz, 3 H), 1.49–1.61 (br, 2 H), 1.62–1.78 (br, 2 H), 1.98–2.18 (br, 3 H), 2.24–2.42 (m, 1 H), 2.46–2.62 (br, 1 H), 3.16–3.32 (m, 1 H), 3.69 (s, 3 H), 4.21 (q, *J* = 7.3 Hz, 2 H), 5.09 (dt, *J* = 4.3 and 2.3 Hz, 1 H), 5.51 (dd, *J* = 11.6 and 5.6 Hz, 1 H), 6.66 (dt, *J* = 4.3 and 2.3 Hz, 1 H) IR (KBr): 1710 cm^{-1}. HRMS (EI): calcd for $C_{15}H_{21}NO_4$, 279.1471; found, 279.1487.

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