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苯乙烯不对称三羰化反应一步合成手性2-氧代-3-苯基戊二酸二甲酯

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摘要: 以苯乙烯、甲醇和CO为反应物, 首次采用双膦配体(*S*)-P-PHOS和乙酰丙酮钯原位制备的手性络合物新催化体系, 以对苯醌作为氧化剂, 对甲苯磺酸作助催化剂, 在甲醇溶剂中进行不对称三羰化反应一步合成手性2-氧代-3-苯基戊二酸二甲酯. 与现有文献结果相比, 三羰化反应所需CO压力明显降低, 条件较为温和.

关键词: 苯乙烯; 不对称三羰化; 手性; 2-氧代-3-苯基-戊二酸二甲酯; 乙酰丙酮钯; 双膦配体
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One-Step Synthesis of Chiral Dimethyl 2-Oxo-3-phenyl-glutarate in the Asymmetric Triple-carbonylation of Styrene

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Abstract: The in-situ preparation of the novel chiral catalyst precursor, which are composed of (*S*)-2,2',6,6'-tetramethoxy-4,4'-bis(diphenylphosphine)-3,3'-bipyridine ((*S*)-P-PHOS) and palladium 2,4-pentanedionate, have been described. These complexes were found to be effective in the asymmetric triple-carbonylation of styrene, reaching up to $[\alpha]_D^{20}$ = +27° (c, 0.28, CH_2Cl_2) for dimethyl 2-oxo-3-phenyl-glutarate using benzoquinone as oxidant, *p*-toluenesulfonic acid as co-catalyst, and methanol as solvent.

Key words: styrene; asymmetric triple-carbonylation; chiral; dimethyl 2-oxo-3-phenyl-glutarate; palladium 2,4-pentanedionate; dipyridlphosphines

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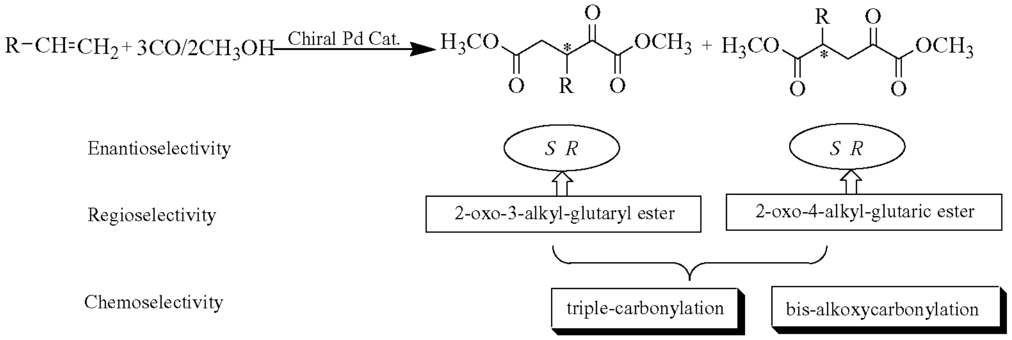
手性的3-烃基-戊二酸酯是合成抗肿瘤药物“利索新”的中间体[1], 也是日本山茶的主要组份, 具有重要的生物活性[2]. 目前, 人们以碘化亚铜为催化剂, 在过量的三甲基氯硅烷存在下, 采用戊二酸二甲酯和格氏试剂反应制备外消旋的3-烃基-戊二酸酯[3], 再经猪肝脂酶催化水解拆分外消旋的产物[4~6]. 比较而言, 以α-烯烃和CO为原料, 手性金属络合物为催化剂, 经三羰化反应 (图式 1), 高活性、高化学选择性、区域选择性和对映选择性, 一步合成 2-氧代-3-烃基-戊二酸酯或 2-氧代-4-烃基-戊二酸酯, 具有重要的应用前景.

1996 年 Sperrle 等[7]首次报道苯乙烯、甲醇和CO的不对称三羰化反应, 他们以手性钯络合物 $[Pd(H_2O)_2\{(S)\text{-MeO-BIPHEP}\}](OTf)_2$(配体 (*S*)-MeO-

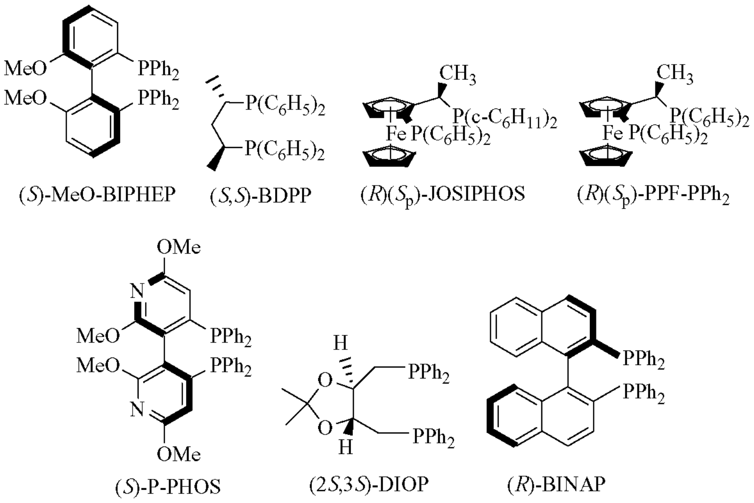
BIPHEP 结构见图式 2) 为催化剂, 反应产物为手性 2-氧代-戊二酸二甲酯, 但其化学选择性低, 且 CO 压力高达 35 MPa. 2000 年, 他们[8]改用手性钯络合物 $[\mathrm{Pd(H_2O)_2}\{(S)\text{-MeO-BIPHEP}\}](\mathrm{BF_4})_2$ 为催化剂, 三羰化反应产物的选择性提高到 32%; 以 $[\mathrm{Pd(H_2O)_2}\{(S)\text{-MeO-BIPHEP}\}](\mathrm{OTf})_2$ 为催化剂, 同时降低氧化剂苯醌用量, 产物选择性增至 37%, 但底物转化率降低, 以苯乙烯为底物的化学选择性要比脂肪族 α-烯烃的高, 另外, CO 压力的升高和催化剂浓度的降低有助于提高反应的化学选择性. 当底物分别为 4-甲基-1-戊烯和 3-苯基-1-丙烯时,反应活性明显降低,三羰化产物化学选择性和区域选择性都较低, 2-氧代-3-甲基-戊二酸酯的对映选择性中等[8]; 以丙烯为底物, 配体 (*S*,*S*)-BDPP 比阻转异构的手性双膦配体 (见图式 2) 诱导的三羰化产物对映选择性低很多. 事实上, (*S*,*S*)-BDPP 与中心金属 Pd 形成六元环络合物, 而阻转异构的手性双膦配体与中心金属 Pd 形成七元环络合物, 前者的刚性要比后者差得多[9,10]; 当配体中磷原子上苯基被环己基取代, 三羰化产物的化学选择性和区域选择性都降低, 二茂铁基手性配体 (*R*) (S_p)-JOSIPHOS 与 (*R*) (S_p)-PPF-$\mathrm{PH_2}$ (见图式 2) 相比, 后者的化学选择性和区域选择性更高.

目前为止, 钯络合物催化的不对称三羰化反应所得产物的化学选择性均有待提高, 且反应条件苛刻, CO 压力高达 9~35 MPa. 因此, 寻找新的不对称三羰化反应催化体系, 降低 CO 压力、高选择性地合成手性 2-氧代-戊二酸酯具有重要意义. 更重要的是, 三羰化反应 (图式 3) 和双羰化 (图式 4) 具有相同的反应中间体, 以此为基础, 考察三羰化反应区域选择性和对映选择性, 比较双羰化产物对映异构体过剩值, 分别采用苯乙烯、丙烯和 4-甲基-1-戊烯等不同底物, 在同样的手性催化剂条件下, 考察三羰化



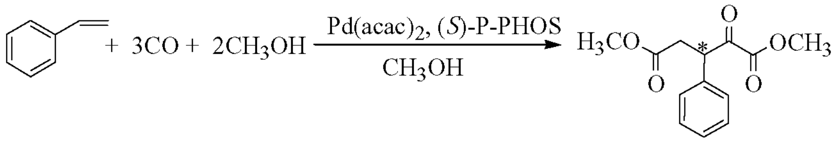
图式 1 α-烯烃的不对称三羰化反应

Scheme 1. Asymmetric triple-carbonylation of α-olefins.



图式 2 手性双膦配体

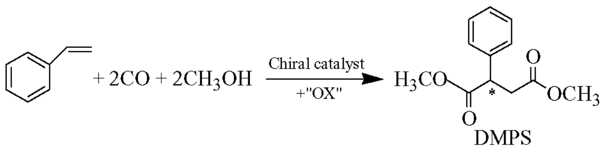
Scheme 2. Chiral bidentatephosphine ligands.



图式 3　苯乙烯不对称三羰化反应

Scheme 3. Asymmetric triple-carbonylation of styrene.

和双羰化反应产物的绝对构型和对映选择性; 或选择同一个底物, 在不同的手性催化体系下, 考察三羰化和双羰化反应产物的对映选择性和绝对构型, 可以阐述羰基化反应机理[9,10], 揭示反应条件对羰基化反应的影响规律. 因此, 本文首次选择手性膦配体 (*R*)-P-PHOS (见图式 2) 与 Pd 形成的络合物为催化剂前体, 研究苯乙烯的三羰化反应, 并与其双羰化反应进行比较.



图式 4　苯乙烯不对称双羰化反应

Scheme 4. Enantioselective bis-alkoxycarbonylation of styrene.

手性膦配体 (*S*)-P-PHOS 为白色粉末状固体, 空气中可稳定存在, 广泛用于不对称催化反应中[11~13]. 以苯乙烯为底物, 手性膦配体 (*S*)-P-PHOS 与醋酸钯 ($Pd(OAc)_2$) 原位制备催化剂, 苯醌为氧化剂, 对甲苯磺酸为助催化剂, 甲醇为溶剂, 此时未发生苯乙烯三羰化反应, 而以乙酰丙酮钯代替醋酸钯时, 则可发生, 生成手性 2-氧代-3-苯基戊二酸二甲酯. 这可能是由于 2 种 Pd 前体和 (*S*)-P-PHOS 原位形成的络合物不同所致.

典型的三羰化反应过程如下[7,8]: 在 100 ml Shlenk 瓶中加入乙酰丙酮钯 (0.025 mmol, 8.4 mg)、手性配体 (*S*)-P-PHOS (0.025 mmol, 16.0 mg) 和甲醇 (4 ml), 磁力搅拌下原位制备手性催化剂. 向 100 ml 高压釜中加入苯乙烯 (5 mmol, 1 ml)、苯醌 (5 mmol, 540 mg)、对甲苯磺酸 (0.05 mmol, 8.6 mg). 在 N_2 保护下, 将上述制得的催化剂溶液转移至高压釜中. 密封高压釜, 用 N_2 置换 3 次后, 通入 CO 升压至 5.5 MPa, 于 50 ºC 油浴中反应 38 h 后, 冷却至室温, 放空釜内未反应的气体, 反应混合液呈金黄色, 有少许黑色沉淀, 用甲醇洗涤反应釜 2 次, 合并洗涤液, 反应混合溶液变混浊, 旋转蒸发溶剂, 有金黄色固体析出, 加入甲苯、搅拌、过滤, 滤液干燥, 减压蒸除溶剂 (0.08 MPa, 90 ºC), 得到油状粗产物 1.13 克, 苯乙烯转化率为 90.4%. 硅胶 (300 目) 柱层析分离, 洗脱液为石油醚 (30~60 ºC)/乙酸乙酯,得产物手性 2-氧代-3-苯基戊二酸二甲酯 50 mg, 其选择性为 4.4%.

^{1}H NMR 谱和 ^{13}C NMR 谱使用 Bruker AM400 型核磁共振仪测定, TMS 作内标; 采用 GC-MS (HPG 1800CGCD) 测定产物的分子量, 样品的比旋光度测定使用 Perkin Elmer 旋光仪 (Model 341 LC).

2-氧代-3-苯基戊二酸二甲酯的表征数据如下: ^{1}H NMR: 2.70 (dd, 1H, CH_2COOR; *J* = 16.0, *J* = 4.0), 3.20 (dd, 1H, CH_2COOR; *J* = 16.0, *J* = 9.8), 3.50 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 4.77 (m, 1H, CH; *J* = 4.0, *J*= 9.8); 7.18–7.22 (m, 5H, C_6H_5). ^{13}C NMR: 35.0 (CH_2COOR), 48.0 (CH), 50.0 (OCH_3), 52.0 (OCH_3), 125.8, 126.4, 128.0, 130.3 (C_6H_5), 157.3 (COCOOR), 169.5 (CH_2COOR), 189.2 (CO). MS (*m*/*z*, relative intensity (%)): 191 (43), 163 (37), 131 (11), 122 (11), 121 (100), 104 (21), 103 (16), 91 (11), 78 (8), 77 (13), 59 (11), 51 (3). 比旋光为: $[\alpha]_D^{20}$ = +27° (c, 0.28, CH_2Cl_2).

以 (*R*)-P-PHOS 为手性配体, 甲苯为溶剂, 于 70 °C 与二苯乙腈二氯化钯进行络合反应合成钯络合物 {(*R*)-P-PHOS}$PdCl_2$; 以四氢呋喃为溶剂, 在无光条件下, 钯络合物 {(*R*)-P-PHOS}$PdCl_2$ 与三氟甲磺酸银反应, 析出 AgCl 沉淀, 合成催化剂前体 [Pd{(*R*)-P-PHOS}$(H_2O)_2$]$(OT_f)_2$: MS (5.68 × 10^4 eV) *m*/*z* (relative intensity (%)): 785 (12), 787 (10) [M-(2 × OTf)]$^+$, 861 (29), 862 (68), 863 (100), 865 (65), 867 (33), 868 (13). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.57 (s, 6H, OCH_3), 3.73 (d, 6H, OCH_3), 6.19 (d, 2H, PyH), 7.41–7.92 (m, 20H, PhH). ^{31}P NMR ($CDCl_3$, 202 MH_Z): δ 30.62. 以苯乙烯为底物, 甲醇为溶剂, 经过数次尝试, 成功实现苯乙烯的双羰化反应 (图式 4), 制得 2-苯基琥珀酸二甲酯 (DMPS).

表 1 钯催化的α-烯烃不对称羰基化反应

Table 1 The asymmetric carbonylation of α-olefins catalyzed by palladium complexes

Entry	Substrate	Catalyst	Conversion (%)	Selectivity (%)	Regioselectivity (%)	$[\alpha]_D^{20}$ or ee
1[a]	styrene	$[Pd\{(S)\text{-P-P}\}(acac)_2]$	90.7	4.4	100/0	+27° (c, 0.28, CH_2Cl_2)
2[b]	styrene	$[Pd\{(R)\text{-P-P}\}(H_2O)_2](OT_f)_2$	24.0	16.0	MC 2.2, MP 1.9	88% (*R*)
3[c]	propene	$[Pd\{(R)\text{-P-P}\}(OAc)_2]$	24g/g-Pd	H-H/H-T/T-T (%) = 17:66:17		+1.4° (c, 0.5, CH_2Cl_2)

[a] Reaction conditions: 0.025 mmol 8.4 mg $Pd(acac)_2$, 0.025 mmol 16.0 mg (*S*)-P-PHOS, methanol 4 ml, styrene 5 mmol, benzoquinone 5 mmol, *p*-toluenesulfonic acid 0.05 mmol, CO 5.5 MPa, 50 ºC, 38 h.

[b] Reaction was operated according to a reported procedure[14].

[c] Pd-catalyzed asymmetric alternating copolymerization of propene and CO was operated according to a reported procedure[15,16].

MC–Methyl cinnamate.

MP–Methyl 2-phenylpropionate and methyl 3-phenyl-propionate.

典型的双羰化反应过程如下[14]: 在 N_2 气氛下, 在 50 ml 的不锈钢高压釜中加入 1.8 mmol 苯乙烯, 1.8 mmol 的 1,4-苯醌, 1.8 × 10^{-3} mmol 的 $[Pd\{(R)\text{-P-PHOS}\}(H_2O)_2](OTf)_2$ 催化剂前体和 1 ml 甲醇, 充 CO 至 15.2 MPa, 于 50 °C 磁力搅拌反应 24 h 后, 冷却至室温, 将反应釜泄至常压, 减压抽干甲醇, 再加入甲苯, 过滤, 滤液中加入内标苯乙酮, 迅速进行气相色谱分析, 毛细管色谱柱为 AT-1 (25 m × 0.25 mm), 以此算得苯乙烯转化率和产物选择性; DMPS 的对映异构体过剩值通过气相色谱分析算得, 手性毛细管色谱柱为 Chrompack Chirasil-DEX CB (50 m × 0.25 mm), 产物的绝对构型通过测定比旋光, 并与文献值比较获得. 结果表明, 苯乙烯转化率为 24.0%, 对映选择性为 88.0% (*R*), 化学选择性为 16.0%, 而副产物为肉硅酸甲酯 (MC, 2.2%), 2-苯基丙酸甲酯和 3-苯基丙酸甲酯 (MP, 1.9%), 以及分子量较低的聚酮[14].

事实上, 苯乙烯双羰化和三羰化反应所用配体和中心金属相同 (表 1, 实验 1 和 2), 但后者加入对甲苯磺酸助催化剂, 导致苯乙烯与中心金属 Pd 配位健之间发生连续 3 次羰基插入, 合成手性的 2-氧代-3-苯基戊二酸二甲酯, 与文献[7,8]结果相比, 化学选择性相对较低, 但所需 CO 压力由 9~35 MPa 降至 5~7 MPa, 可见反应条件相对温和. 苯乙烯双羰化和三羰化反应结果相比, 两者均生成分子量较低的聚酮. 因此, 本文以苯乙烯、甲醇和 CO 为反应物, 在催化剂前体$[Pd\{(R)\text{-P-PHOS PP}\}(OAc)_2]$存在下, 尝试一步不对称多羰化反应-苯乙烯与 CO 不对称交替共聚反应合成较高分子量的手性聚酮, 但没有成功; 以丙烯代替苯乙烯为底物, 使用上述催化剂体系, 在有机溶剂或离子液体介质中, 合成手性功能高分子聚酮[15,16], 共聚物的数均分子量 $M_n = 0.97 \times 10^3$, 分散度 $M_w/M_n = 4.4$, 显示高的区域规整度 H-H/H-T/T-T (%) = 17:66:17 (表 1, 实验 3).

综上可见, 以苯乙烯、甲醇和 CO 为反应物, 采用双膦配体 (*S*)-P-PHOS 和乙酰丙酮钯原位制备的手性络合物新催化体系, 以对苯醌作为氧化剂,对甲苯磺酸作助催化剂, 在甲醇溶剂中,通过不对称三羰化反应一步合成手性 2-氧代-3-苯基戊二酸二甲酯.

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英 译 文

English Text

As the intermediate of Rhizoxin synthesis [1] and the main component of Sophora japonica [2], chiral 3-alkyl-glutaryl ester has significant biological activity. Up to now, the synthesis of chiral 3-alkyl-glutaryl ester is as follows, the racemic 3-alkyl-glutaric esters are synthesized using CuI as the catalyst through the reaction of dimethyl glutarate and the Grignard reagent in the presence of excessive trimethylchlorosilane [3], and then the products are obtained through the hydrolysis of resolution of racemic 3-alkyl-glutaric esters by catalytic hydrolysis using liver lipase [4–6]. Asymmetric triple-carbonylation of α-olefin is shown in Scheme 1. 2-Oxo-3-alkyl-glutaryl ester and/or 2-oxo-4-alkyl-glutaric ester were synthesized through triple-carbonylation with high activity, high chemoselectivity, regioselectivity, and enantioselectivity using α-olefins as substrates and chiral metal complexes as catalysts.

Enantioselective triple-carbonylation of styrene was for the first time reported by Sperrle et al [7] in 1996 using palladium complexes $[Pd(H_2O)_2\{(S)\text{-MeO-BIPHEP}\}](OTf)_2$ as chiral catalyst and methanol as reactants and solvent. The structure of ligand (*S*)-MeO-BIPHEP is shown in Scheme 1. Product dimethyl 2-oxo-3-phenyl-glutarate was received. However, the chemical selectivity of the reaction was low, and CO pressure of reaction was up to 35 MPa. In 2000, Sperrle et al [8] used palladium complex $[Pd(H_2O)_2\{(S)\text{-MeO-BIPHEP}\}](BF_4)_2$ as catalyst precursor, and the selectivity for triple carbonylation increased to 32%. The use of complex $[Pd(H_2O)_2\{(S)\text{-MeO-BIPHEP}\}](OTf)_2$ as the catalyst and reducing the amount of benzoquinone could make the selectivity increase to 37%, but the conversion of the reaction decreased. Using styrene as substrate, the chemical selectivity of reaction was higher than that of aliphatic α-olefins. The chemical selectivity of reactions could be improved by increasing CO pressure and reducing the concentration of the catalyst. When 4-methyl-1-pentene and 3-phenyl-1-propylene as substrates were used, respectively, the conversion of reaction was significantly reduced, the chemoselectivity and regioselectivity of triple carbonylation were relatively low, and the enantioselectivity of 2-oxo-3-methyl-glutaryl esters was moderate [8]. When propylene as the substrate was employed, ligand (*S*,*S*)-BDPP afforded lower enantioselectivity of triple carbonylation than enantiopure atropoisomeric bidentatephosphine ligands (Scheme 1). In fact, ligand (*S*,*S*)-BDPP and Pd can form six-membered ring complexes, while enantiopure atropoisomeric bidentatephosphine ligands and Pd form seven-membered ring intermediate. The rigidity of the former is much less than that of the latter [9,10]. When the phenyl group on the phosphorus of enantiopure atropoisomeric bidentatephosphine ligands is substituted, chemoselectivity and regioselectivity of triple carbonylation were reduced. As for chiral ligands (*R*) (S_p)-JOSIPHOS and (*R*) (S_p)-PPF-PH_2 (Scheme 2) based on ferrocenyl, the latter's chemoselectivity and regioselectivity is higher than that of the former. So far, the chemical selectivity of the asymmetric triple-carbonylation reaction catalyzed by palladium/bidentatephosphine ligands complexes needs to be enhanced, and CO pressure needs to be reduced. Therefore, the research on a novel catalytic system of the asymmetric triple-carbonylation has a great significance.

Triple-carbonylation has the methodological importance. More importantly, triple-carbonylation (Scheme 3) and bis-alkoxycarbonylation (Scheme 4) have the same intermediates of reaction. This can be used as a basis to study the regio- and enantioselectivity of triple-carbonylation. In contrast with enantioselectivity of triple-carbonylation and bis-alkoxycarbonylation and the absolute configuration of product, using various substrates such as styrene, propylene, and 4-methyl-1-ene in the same chiral catalyst and selecting the same substrate in different chiral catalyst systems, can optimize the reaction conditions, and deduce the mechanism of carbonylation [9,10]. For the first time this work employs ligands (*S*)-P-PHOS (Scheme 2)/Pd complex as catalyst precursor to investigate triple-carbonylation of styrene.

Phosphine ligand (*S*)-P-PHOS as a white solid powder, stable in air, has been successfully applied in asymmetric catalytic reactions [11–13], such as asymmetric hydrogenation of dehydrogenation amino acids and prochiral aromatic ketones. When styrene was used as the substrate, ligand (*S*)-P-PHOS and palladium acetate ($Pd(OAc)_2$) were used to in situ prepare the chiral catalysts, in the presence of *p*-benzoquinone as the oxidant, *p*-toluenesulfonic acid as co-catalyst, and methanol as solvent, triple-carbonylation of styrene did not occur. However, when $Pd(OAc)_2$ was replaced with acetylacetonate Palladium ($Pd(acac)_2$), it was interesting that triple-carbonylation of styrene occurred, and chiral 2-oxo-3-phenyl dimethyl glutarate was obtained by column chromatography of the crude product. This may be due to various catalytic precursor using ligand (*S*)-P-PHOS/$Pd(OAc)_2$ or $Pd(acac)_2$ formed in situ.

The typical reaction procedure of triple-carbonylation is as follows [7,8], a mixture of $Pd(acac)_2$ (0.025 mmol, 8.4 mg), (*S*)-P-PHOS (0.025 mmol, 16.0 mg), styrene (5 mmol, 1 ml), benzoquinone (5 mmol, 540 mg), *p*-toluenesulfonic acid (0.05 mmol, 8.6 mg) in methanol (4 ml) was stirred under nitrogen for 1 h at room temperature. A 100 ml stainless steel autoclave was dried, purged with N_2, the above methanol solution was transferred into it. After sealing autoclave, CO

(5.5 MPa) was introduced. The reaction mixture was heated to 50 ºC in oil bath and stirred for 38 h. At the end of triple-carbonylation, autoclave was cooled to room temperature, and the residual gas was released safely. The reaction mixture became brown and there existed a little black precipitate. The autoclave was washed with methanol, and the washing liquid was combined, which made the reaction mixture turbid. After removing of the methanol from the reaction mixture under reduced pressure, toluene was added, causing most of the hydroquinone to precipitate. The filtrate was evaporated, and oily crude product (1.13 g) was purified by column chromatography over silica (300 mesh) using petroleum ether (30–60 ºC)/ethyl acetate as the eluent. The conversion of styrene is up to 90.4%. A 50 mg of 2-oxo-3-phenyl dimethyl glutarate was obtained, and the selectivity of the reaction was 4.4%.

^{1}H NMR and ^{13}C NMR were recorded on a Bruker AM400 NMR (TMS as internal standard). GC-MS was performed on a HPG 1800CGCD equipped with FID detector to measure the molecular weight. The specific rotation of the sample was performed using the Perkin Elmer Polarimeter (Model 341 LC).

Characterization data of dimethyl 2-oxo-3-phenyl glutarate is as follows, ^{1}H NMR: 2.70 (dd, 1H, CH_2COOR; $J = 16.0$, $J = 4.0$), 3.20 (dd, 1H, CH_2COOR; $J = 16.0$, $J = 9.8$), 3.50 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 4.77 (m, 1H, CH; $J = 4.0$, $J = 9.8$); 7.18–7.22 (m, 5H, C_6H_5). ^{13}C NMR: 35.0 (CH_2COOR), 48.0 (CH), 50.0 (OCH_3), 52.0 (OCH_3), 125.8, 126.4, 128.0, 130.3 (C_6H_5), 157.3 (COCOOR), 169.5 (CH_2COOR), 189.2 (CO). MS (*m/z*, relative intensity (%)): 191 (43), 163 (37), 131 (11), 122 (11), 121 (100), 104 (21), 103 (16), 91 (11), 78 (8), 77 (13), 59 (11), 51 (3). Specific rotation: $[\alpha]_D^{20} = +27^o$ (c, 0.28, CH_2Cl_2).

Catalyst precursor $[Pd\{(R)\text{-P-PHOS}\}(H_2O)_2](OTf)_2$ was synthesized in the presence of $PdCl_2(NCPh)_2$ and ligand (*R*)-P-PHOS according to a reported procedure [14]. MS (5.68×10^4 eV) *m/z* (relative intensity (%)): 785(12), 787 (10) $[M\text{-}(2 \times OTf)]^+$, 861 (29), 862 (68), 863 (100), 865 (65), 867 (33), 868 (13). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.57 (s, 6H, OCH_3), 3.73 (d, 6H, OCH_3), 6.19 (d, 2H, PyH), 7.41–7.92 (m, 20H, PhH). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 30.62. After several attempts, *bis*-alkoxycarbonylation of styrene was realized successfully (Scheme 4) and dimethyl 2-phenyl succinate (DMPS) was synthesized using methanol as solvent.

A typical procedure [14] for enantioselective *bis*-alkoxycarbonylation of styrene is as follows, 50 mL stainless steel autoclave was dried, purged with N_2. It was charged with 1.8 mmol of styrene, 1.8 mmol of 1,4-benzoquinone, and 1.8×10^{-3} mmol of $[Pd\{(R)\text{-P-PHOS}\}(H_2O)_2](OTf)_2$ catalyst precursors, and 1 ml of methanol under an atmosphere of N_2. It was pressurized with CO (15.2 MPa), heated to 50 °C. The reaction mixture was stirred well with a magnetic stirrer. After a prescribed period of 24 h, the reactor was cooled to room temperature, and the remaining CO was released safely. Solvent methanol was removed in vacuum, followed by the addition of toluene causing the precipitation of solid hydroquinone. The mixture was filtered, and the filtrate was purified by column chromatography. The data on conversion and selectivity were determined immediately by GC on an AT-1 capillary column (25 m × 0.25 mm i.d.) using acetophenone as an internal standard. The enantiomeric excess of triple-carbonylation of styrene was analyzed by GC using a Chrompack Chirasil-DEX CB (50 m × 0.25 mm i.d.). The absolute configuration of the product was determined by measuring the specific rotations in comparison with literature values. The conversion of styrene to DMPS was only 24.0%. A 88.0% (*R*) enantioselectivity and 16.0% chemoselectivity for DMPS, 2.2% chemoselectivity for ethyl cinnamate (MC) and 1.9% chemoselectivity for methyl 2-phenylpropionate and methyl 3-phenyl-propionate (MP) were received. By-product with low molecular weight such as polyketone was formed [14].

In the above-mentioned bis-alkoxycarbonylation and triple-carbonylation of styrene, ligands, and the central metal are the same (Table1, entries 1–2). Difference is as follows, *p*-toluenesulfonic acid as co-catalyst in triple-carbonylation was employed. Thus, three consecutive carbonyl insertions between coordination bond of styrene and Pd center occurred, and chiral 2-oxo-3-phenyl dimethyl glutarate was synthesized. In contrast to the literature results [7,8], chemical selectivity is relatively low and CO pressure (5–7 MPa) was reduced. In the triple-carbonylation of styrene, the reaction conditions were mild. It was found that by-product with low molecular weight such as polyketone was formed in the above-mentioned bis-alkoxycarbonylation and triple-carbonylation of styrene. It is noteworthy that asymmetric alternative copolymerization of styrene and CO did not occur in the presence of $[Pd\{(R)\text{-P-PHOS PP}\}(OAc)_2]$ as catalyst precursor. But using $[Pd\{(R)\text{-P-PHOS PP}\}(OAc)_2]$ as catalyst precursor, asymmetric alternative copolymerization of propylene and CO in organic solvent and/or ionic liquid gave chiral polyketones [15,16], with $M_n = 0.97 \times 10^3$, $M_w/M_n = 4.4$, and regioregularity of HH/HT/TT (%) = 17:66:17 (Table 1, entry 3).

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