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A Convenient Method for the Preparation of Inverted *tert*-Alkyl Carboxylates from Chiral *tert*-Alcohols by a New Type of Oxidation−Reduction Condensation Using 2,6-Dimethyl-1,4-benzoquinone

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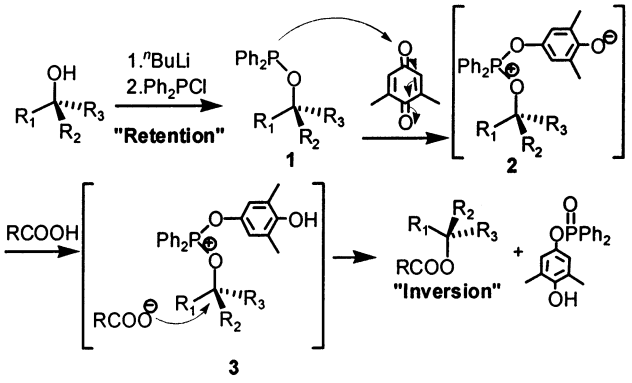
The fundamental concept of oxidation−reduction condensation is to perform dehydration condensation by removing H_2O as in 2[H] and [O] with the use of a combination of weak reductants and oxidants. These reactions proceed under "mild and neutral" conditions without having any assistance of acids or bases. Examples of these innovative acylation reactions using combinations of diphenylmercury and tributylphosphine (1963),[1] *trans*-1,2-dibenzoylethylene and tributylphosphine (1964),[2] and 2,2′-dipyridyl disulfide and triphenylphosphine (1970)[3] were reported from our laboratory. In 1967, phosphoric esters were also prepared by using triethyl phosphite and diethyl azodicarboxylate (DEAD) in the presence of alcohols.[4] Mitsunobu further developed this concept to an efficient alkylation method by using a combination of triphenylphosphine and DEAD (Mitsunobu reaction).[5] Recently, Tsunoda et al. reported an alkylation reaction using alcohols and cyanomethylenetributylphosphorane or *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)[6] which worked out likewise. Shi et al. described stereospecific synthesis of chiral tertiary alkyl−aryl ethers via Mitsunobu reaction with complete inversion of configuration in about 50% chemical yield.[7]

The search for a new combination of weak reductant and oxidant in oxidation−reduction condensation has been a matter of our continued interest ever since the reaction was first reported. Quinone compounds have long been anticipated as effective oxidants in this type of condensation; however, no examples have been shown to be successful to date. We consider that an interaction of alkoxydiphenylphosphine with weak oxidants such as quinone should provide a key intermediate, phosphonium salt, more smoothly than triphenylphosphine because of the increased reducing ability.[8]

It has been shown that oxidation−reduction condensation using a combination of 2,6-dimethyl-1,4-benzoquinone and alkoxydiphenylphosphines, formed in situ from alcohols and chlorodiphenylphosphine or (*N*,*N*-dimethylamino)diphenylphosphine, affords alkyl carboxylates in high yields from the corresponding alcohols and carboxylic acids by a one-pot procedure.[9] The esterification of various secondary alcohols proceeded similarly to afford the corresponding esters in high yields with perfect inversion of stereochemistry.[9] Further, it was shown that the reactions of various carboxylic acids with in situ-formed tertiary alkoxydiphenylphosphines, for example, 2,2-dimethylpropionic acid and 2-methyl-1-phenylpropan-2-ol, or 2-phenylbutyric acid and 1-adamantanol, afforded the corresponding *tert*-alkyl carboxylates in 85−96% yields, respectively.[9] The possibility of inversion of the *tert*-alkyl alcohol in this ester-forming reaction was then considered.

This Communication describes a new oxidation−reduction method for converting tertiary alcohols into their corresponding esters with almost complete inversion of configuration. The method involves initial conversion of the alcohol to its diphenylphosphinite ester, followed by treatment with the carboxylic acid and 2,6-dimethyl-1,4-benzoquinone (Scheme 1).

Scheme 1. Formation of Inverted *tert*-Alkyl Carboxylic Esters from Chiral *tert*-Alcohols



Results for the present condensations of carboxylic acids with various chiral tertiary alcohols are shown in Table 1. Alkylation of carboxylic acids proceeded smoothly in dichloromethane at room temperature to afford the corresponding *tert*-alkyl carboxylates in good yields with almost complete inversion of stereochemistries, while the corresponding ester was obtained in 83% yield with the retention of stereochemistry by reaction in a CH_2Cl_2 solution of 1-adamantanol and benzoic acid for 15 h (Table 1, entry 1). In the case of using benzoic acid or *p*-methoxybenzoic acid having an electron-donating group, the esterifications using various chiral tertiary alcohols proceeded within 18 h at room temperature to afford the corresponding alkyl esters in good yields (81−90%) with almost complete inversion of stereochemistries (98 to >99%) (Table 1, entries 4, 5, 8, 9, and 12−14). When aliphatic carboxylic acid or *p*-chlorobenzoic acid having an electron-withdrawing group was used, on the other hand, the desired esters were obtained in 76−86% yields with 70−84% inversion (Table 1, entries 6, 7, 10, and 11). By refluxing a CH_2Cl_2 solution of (−)-terpinen-4-ol and benzoic acid or 3-phenylpropionic acid for 15 h, the desired esters were obtained in 78% yield with 98% inversion or 76% yield with 40% inversion, respectively (Table 1, entries 2 and 3), whereas the corresponding olefin was formed in 81% yield in the case of 2-(4-methoxyphenyl)-2-butanol, and none of the desired esters were detected (Table 1, entry 15).

Thus, oxidation−reduction condensation using alkoxydiphenylphosphine (i.e., diphenylphosphinite ester) generated in situ 2,6-dimethyl-1,4-benzoquinone, and carboxylic acids provide a new and efficient method for the preparation of inverted *tert*-alkyl carboxylates from various chiral tertiary alcohols.

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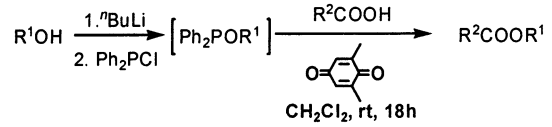
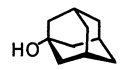
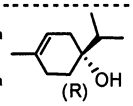
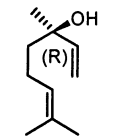
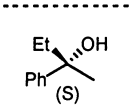
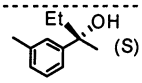
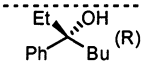
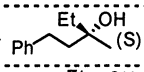
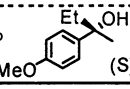
Table 1. Esterification between Several Carboxylic Acids and Various Chiral Tertiary Alcohols[12]



Entry	R^1OH[c]	R / S[d]	R^2	Yield /%	R / S[e]	Inversion /%
1[a]			Ph	83		0
2[a]		86 / 14	Ph	78	16 / 84	98
3[a]			$PhCH_2CH_2$-	76	66 / 34	40
4		95 / 5	Ph	85	7 / 93	98
5			*p*-MeO-C_6H_4-	86	5 / 95	>99
6			*p*-Cl-C_6H_4-	83	20 / 80	84
7			$PhCH_2CH_2$-	76	24 / 76	80
8		2 / 98	Ph	90	98 / 2	>99
9			*p*-MeO-C_6H_4-	88	98 / 2	>99
10			*p*-Cl-C_6H_4-	86	70 / 30	71
11			$PhCH_2CH_2$-	86	69 / 31	70
12		1 / 99	Ph	86	99 / 1	>99
13		91 / 9	Ph	83	9 / 91	>99
14		22 / 78	Ph	81	77 / 23	99
15[b]			Ph	N.D.		

[a] The reaction mixture was refluxed for 15 h. [b] The corresponding olefin was obtained in 81% yield. [c] Entries 2−7: chiral alcohols of (−)-terpinen-4-ol (Acros Organics) and (−)-linalool (Fluka Chemika) were purchased according to Walsh's procedure.[11] See Supporting Information. [d] The enantiomeric ratios of *tert*-alcohols were determined by preparing the corresponding esters with the carboxylic chlorides. See ref 10. [e] The conditions of separating the corresponding esters were shown in Supporting Information.

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Supporting Information Available: Experimental procedures and characterization of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935.

(5) For example, see: (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380. (b) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427. (c) Mitsunobu, O. *Synthesis* **1981**, 1. (d) Hughs, D. L. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1992; Vol. 42, p 335.

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(10) It is generally known that it is difficult to prepare even *tert*-alkyl carboxylates in high yield with retention. The corresponding carboxylic acid esters were afforded in 20−50% yields with retention of stereochemistry by using of lithium tertiary alkoxide and carboxylic acid chloride; see: Crowther, G. P.; Kaiser, E. M.; Woodruff, R. A.; Hauser, C. R. *Org. Synth.* **1988**, *IV*, 259.

(11) Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970.

(12) Typical experimental procedure: Into a stirred solution of chiral *tert*-alcohol (1.5 mmol) in THF (5 mL) was dropped a hexane solution of ^{n}BuLi (1.5 mmol) at 0 °C under argon atmosphere. After the solution was stirred at room temperature for 1.0 h, a THF (2 mL) solution of chlorodiphenylphosphine (1.5 mmol) was added at 0 °C. The reaction mixture was stirred for 1.0 h at room temperature, and the solvent was concentrated in vacuo. Immediately, carboxylic acid, DMBQ, and dichloromethane were added to the residue, and the mixture was stirred for 18 h at room temperature. The same result was alternatively obtained by the following procedure: that is, after the above-mentioned residue was diluted with a mixed solution of hexane (3 mL) and ethyl acetate (0.5 mL), lithium chloride was removed by filtration through Celite (1.0 g) after the residue was passed through alumina (activated, basic) (Wako Pure Chemical Industries, LTD) (7 g). The solvent was concentrated in vacuo, and crude alkoxydiphenylphosphine was obtained. To a mixture of carboxylic acid (0.60 mmol) and DMBQ (0.60 mmol) under argon atmosphere was added a dichloromethane (0.50 mL) solution of the above crude alkoxydiphenylphosphine under above condition. After the reaction that was monitored by TLC was completed, the reaction mixture was quenched by adding water, and the aqueous layer was extracted with dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate. After filtration and evaporation, the resulting residue was purified by preparative TLC to afford the corresponding carboxylic esters.

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