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Dimethylmalonyltrialkylphosphoranes: probing the steric effect on phosphorus and its stereochemical consequence in esterification reactions of chiral secondary alcohols

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Abstract

High chemical yields and high levels of stereochemical inversion are demonstrated in the phosphorane-mediated esterification reaction of chiral alcohols with non-hindered carboxylic acids through the incorporation of sterically non-hindered alkyl groups of phosphorus.

Keywords: Esterification; Trialkylphosphoranes; Stereocontrol

The direct condensation and displacement reactions of alcohols with various nucleophiles can be successfully carried out using the versatile Mitsunobu reaction [1–4]. The Mitsunobu reaction is especially powerful when the inversion of stereochemistry of a chiral secondary alcohol is required. However, the triphenylphosphine oxide and hydrazine side products are notoriously difficult to remove from the product adding considerable time and resources and resulting in lower isolated yields of the substitution product. In addition to its value as a general fragment coupling technique for both inter- and intra-molecular bond formations, the reliable stereocourse of the reaction proceeding with inversion was until recently accepted as the norm. Indeed, many structural assignments have been made with the assumption of inversion occurring during a Mitsunobu reaction which does appear to be so in the vast majority of cases. However, in recent years several accounts reporting retention of stereochemistry have been disclosed [5–8] involving the condensation of sterically hindered secondary alcohols under standard Mitsunobu conditions. A somewhat modified view of the reaction mechanism has evolved outlined in Scheme 1.

The first step in the reaction mechanism involves the nucleophilic addition of triphenylphosphine to the azodicarboxylate followed by proton transfer from the carboxylic acid to give the carboxylate **1a** and activated intermediate **3** as shown in Scheme 1. Since the product ester is by and large the inversion product, the reaction was thought [3,4] to proceed directly to the alkoxyphosphonium ion **4** (Path 1) through alcohol attack on **3**. Nucleophilic displacement by the carboxylate anion on the activated alkoxyphosphonium ion **4** (inversion path) then delivers the inverted ester [2a].

In order to obtain the retention product, a different pathway must also be available. In this case, it has been proposed that the reaction occurs through an

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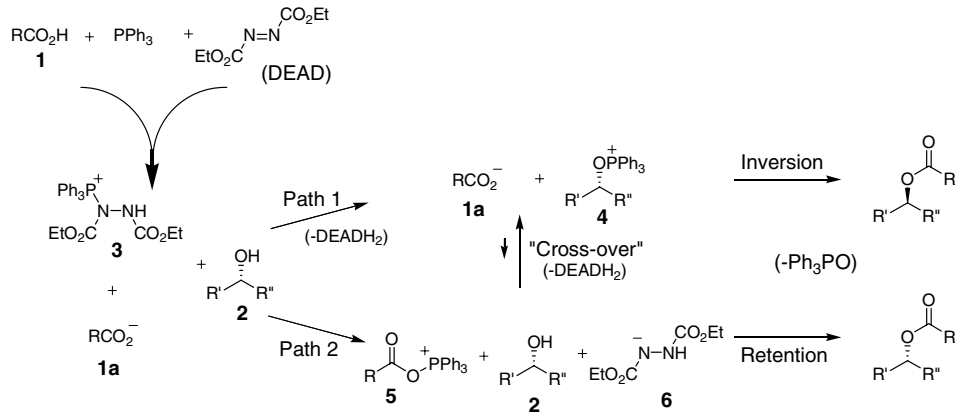


Scheme 1. Mechanism of the Mitsunobu esterification.

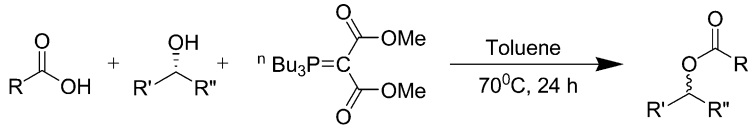
acyloxyphosphonium ion intermediate **5**, described in Path 2. This intermediate is generated by the more nucleophilic carboxylate anion **1a** attacking **3** rather than the alcohol **2**. It was postulated [3b,6] that there may exist a ''cross-over'' reaction pathway mediated by basic species present or generated during the reaction such as the hydrazide anion **6**. Such basic species would be expected to promote the ''cross-over'' step resulting in the formation of **4** leading to the inversion product. This hypothesis was supported by the unambiguous independent generation of acyloxyphosphonium ions [9] and trapping with chiral secondary alcohols under neutral or basic conditions where high levels of retention or inversion of stereochemistry were observed respectively.

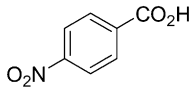
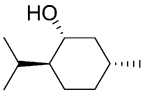
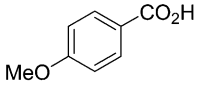
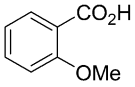
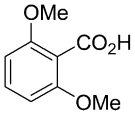
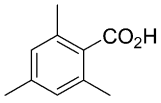
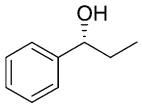
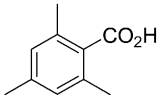
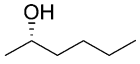
We have been interested in the generation of new phosphonium intermediates having the general structure R_3P^+X (i.e., like **3**), in which R is an alkyl or aryl substituent and X represents a good leaving group (as X^-) of controlled basicity. Other phosphorane reagents, most significantly Tsunoda's cyanomethylene reagents, generate basic anions during the reaction and thus provide results similar to the original Mitsunobu class [10–12] In contrast, our recently [6] reported phosphorane, synthesized from tributylphosphine and chlorodimethylmalonate, produces an intermediate that expels the dimethylmalonyl anion and is therefore significantly less basic than **6**. This tributylphosphorane reagent was shown to promote the general condensation reaction of a wide range of carboxylic acid and alcohol partners, through generation of intermediates analogous to **5** under conditions of controlled reaction basicity, providing esters along with tributylphosphine oxide and dimethylmalonate [6]. In addition to the levels of stereocontrol achievable (vide infra), the side products produced are easily removed by aqueous base partition, eliminating the purification difficulties inherent in the use of standard Mitsunobu reagents.

An extensive survey on the use of this new dimethylmalonyltributylphosphorane reagent on the condensation of a variety of carboxylic acids with chiral secondary alcohols was carried out under a standard set of conditions [6], some key observations are summarized in Table 1. It is evident that electron deficient substituents not only increase the yield but also lead to high levels of retention of stereochemistry in the final product. The position of the substituent on the phenyl group also affects the stereochemical outcome of the reaction, with *ortho* groups increasing the level of inversion in comparison to identical *para* substituents. Use of the mechanistic pathway outlined in Scheme 1 proceeding through the acyloxytri *butyl* phosphonium ion (analogous to **5**) and the base-induced ''cross-over'' allow a rationalization of the overall substituent affects on the stereochemical outcome (Table 1). Electron-rich carboxylic acids are converted to their corresponding carboxylate ions which are expected to be stronger bases when compared with electron-deficient acid. Therefore, electron-rich substituents would be expected to favour the inversion product. In terms of the steric effect, sterically hindered carboxylic acids render attack of the alcohol on the acyl center of the acyloxyphosphonium ion more difficult, allowing increased opportunity for ''cross-over'' and the formation of the alkoxyphosphonium ion leading to a relatively higher degree of inversion. Lastly, with sterically hindered alcohols direct attack at the acyl carbon atom is more likely lessening cross-over to the alkoxyphosphonium ions, thereby favouring the product of retention.

According to the revised mechanism, reaction intermediates of type **5** may be considered ''bifunctional'' reagents that can allow alcohol or alkoxide attack at the phosphorus atom, promoting crossover leading to the normal inversion product, or may function as direct acylating agents through alcohol attack at the carboxyl carbon leading to the product of retention. As one of the most important attributes of the Mitsunobu and related redox condensation processes is the reliable high degree stereocontrol achievable, particularly inversion of stereochemistry, the preparation of analogs of these new

Table 1
Chiral esterification reactions promoted by tri^{n}butylphosphorane analogue



	Acid	Alcohol	Retention : Inversion (Yield)
1			**95:5 (82%)**
2		"	**33:67 (52%)**
3		"	**2:98 (28%)**
4		"	**4:96 (56%)**
5			**5:95 (83%)**
6			**0.1:99.9 (84%)**

phosphoranes being more or less sterically congested around phosphorus became of obvious interest. We accordingly prepared the tri(iso)butyl and triethylphosphorane analogs. While both the ^{n}butyl and (iso)butyl analogs were isolated as viscous oils, the triethylphosphorane proved to be crystalline and as such a single crystal X-ray structural determination was undertaken, Fig. 1, confirming the structure.

To begin with, the reaction of 4-nitrobenzoic acid with both (*2S*)-hexanol and (*1R*)-1-phenylpropanol

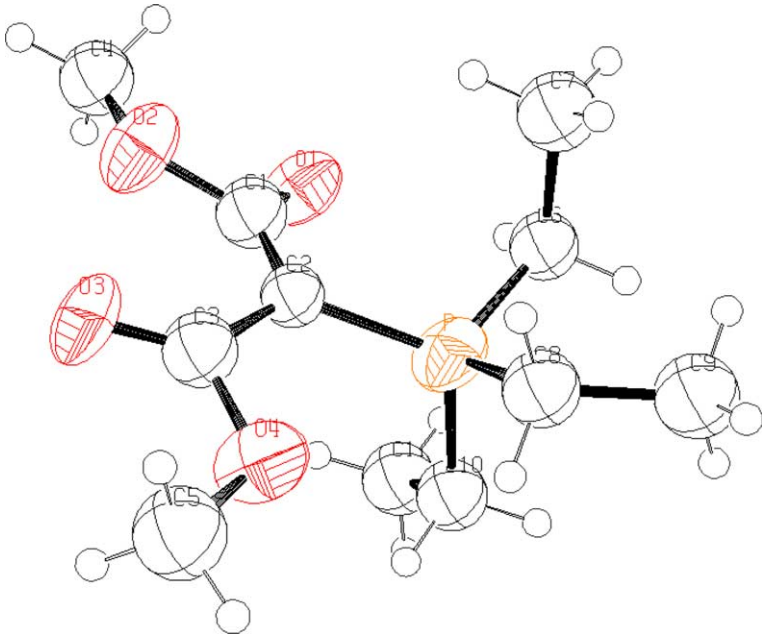
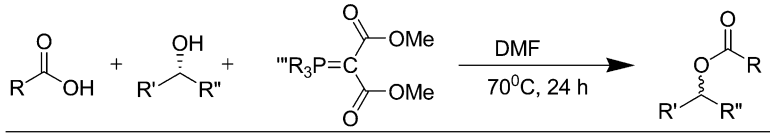
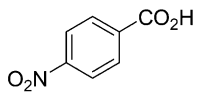
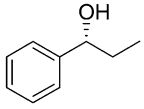
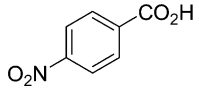
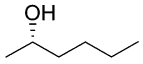


Fig. 1. X-ray structure (ORTEP) of dimethylmalonyltriethylphosphorane showing a distorted tetrahedral geometry about the phosphorus atom.

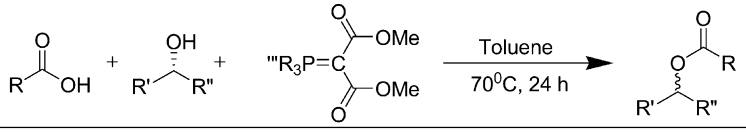
Table 2
Chiral esterification reactions promoted by tri^{iso} and tri^{n}butylphosphorane analogues

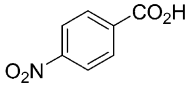
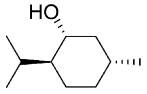
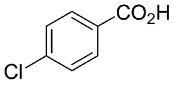
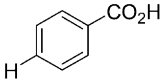
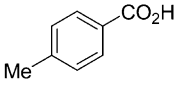
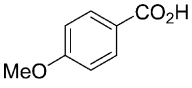
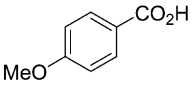
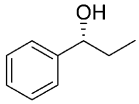
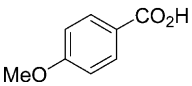
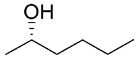


	Acid	Alcohol	Retention : Inversion (Yield) R^{III}=^{i}Bu	R^{III}=^{n}Bu
1			95:5 (27%)	64:36 (61%)
2			97:3 (34%)	80:20 (71%)

using both the *n*-butyl and (iso)butyl phosphoranes was investigated. As can be seen from the results in Table 2, more hindered substituents on phosphorus lead to a higher degree of retention, with all other factors unchanged. The lower yields reflect the overall slower rate of the reaction with the more hindered phosphorane under the standard reaction conditions. These stereochemical results are fully in accord with our mechanistic model in which attack at the phosphorus centre of intermediate **5** becomes less favorable as steric congestion increases on phosphorus leading to more direct acyl transfer and a higher degree of retention of stereochemistry in the resulting ester. The condensation of a series of carboxylic acid and chiral secondary alcohol partners was then investigated with the less sterically congested triethylphosphorane derivative.

Table 3
Chiral esterification reactions promoted by triethyl and tri^{n}butylphosphorane analogues



Entry	Acid	Alcohol	Retention : Inversion (Yield) R^{III} = Et	R^{III} = ^{n}Bu
1			85:15 (72%)	95:5 (82%)
2		"	37:60 (27%)	87:13 (89%)
3		"	24:76 (24%)	81:19 (76%)
4		"	15:85 (24%)	63:37 (53%)
5		"	2:98 (25%)	33:67 (52%)
6			4:96 (73%)	-
7			0.1:99.9 (80%)	-

The reactions of this triethylphosphorane were investigated side by side with the tributyl analog and the results summarized in Table 3. Entries 1 and 2 were conducted under conditions expected to provide a high degree of retention (electron deficient, non-hindered acid). As can be seen, the triethylphosphorane provides a higher degree of inversion even here. Most significantly, entries 4–7 show that high degrees of inversion of configuration can be obtained using the triethylphosphorane for the coupling of chiral secondary alcohols and electron rich, sterically unencumbered acids (no *ortho*-substituents), particularly with the use of 4-methoxybenzoic acid. These results contrast to the use of the tributylphosphorane analog, with which only the use of electron-rich hindered *ortho*-substituted acids provided such high inversions.

Overall, these results clearly demonstrate that the steric bulk of the alkyl groups present on the phosphorus atom of the phosphorane play a significant but predictable role on the stereochemical outcome of the reaction. Less bulky groups favor inversion of stereochemistry while bulky butyl groups favor retention of configuration. These results reported for the uncongested triethylphosphorane provide further structural evidence in full agreement with the current mechanistic picture of the reaction.

In conclusion, the new dimethylmalonyltrialkylphosphorane class of esterification reagent has been extended and the steric effect of the substituent on phosphorus probed. We feel that these reagents have much potential; they are easy to prepare and can be handled in air for short periods of time. They provide halogen, acid and base free reaction media for esterification reactions and thus tolerant of a variety of functional groups. They have been successfully employed in the coupling of a wide range of primary and secondary alcohols with various carboxylic acids [6]. The ester product can be purified with relative ease using as aqueous base-organic partition sequence to remove the water and base soluble side products. Lastly, a major advantage of this new class of reagent is the controlled levels of inversion or retention that can be achieved through careful choice of reagents. To achieve high levels of inversion on a chiral secondary alcohol, two optimum combinations of reagents are recommended. The use of 2,6-disubstituted benzoic acids in conjunction with the tributylphosphorane results in a formation of the corresponding benzoates with chemical yields up to 90% and high inversion. Alternatively, the combination of *p*-methoxybenzoic acid with the triethylphosphorane reagent provides the corresponding inverted *p*-methoxybenzoates with high chemical yields up to 80%. To achieve high levels of retention, the use of the tributylphosphorane or tri(iso)butylphosphorane in conjunction with an electron deficient carboxylic acid appears to be the optimal combination. All of these results are in accord with the modified view [2c] of the mechanism outlined in Scheme 1. Applications of these reagents towards the synthesis of natural products are in progress and will be reported in due course.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.jorganchem.2004.10.046.

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