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Dimethylmalonyltrialkylphosphoranes: New General Reagents for Esterification Reactions Allowing Controlled Inversion or Retention of Configuration on Chiral Alcohols

James McNulty,*,† Alfredo Capretta,† Vladimir Laritchev,† Jeff Dyck,† and Al J. Robertson‡

Institute of Molecular Catalysis, Department of Chemistry, Brock University, St. Catharines, Ontario L2S 3A1 Canada, Cytec Canada Inc., P.O. Box 240, Niagara Falls, Ontario L2E 6T4, Canada

jmcnulty@chemiris.labs.brocku.ca

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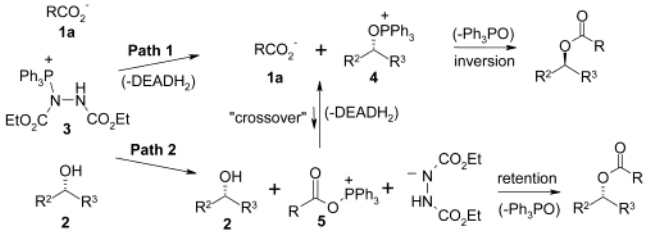
Abstract: A new class of trialkylphosphorane has been prepared through reaction of a trialkylphosphine with 2-chlorodimethylmalonate in the presence of triethylamine. These new reagents promote the condensation reaction of carboxylic acids with alcohols to provide esters along with trialkylphosphine oxide and dimethylmalonate. The condensation reaction of chiral secondary alcohols can be controlled to give either high levels of inversion or retention through a subtle interplay involving basicity of the reaction media, solvent, and tuning the electronic and steric nature of the carboxylic acid and steric nature of the phosphorane employed. A coherent mechanism is postulated to explain these observations involving reaction via an initial acyloxyphosphonium ion.

The Mitsunobu reaction[1−4] is widely employed in both condensation and displacement reactions of alcohols with various nucleophiles, normally proceeding with inversion of stereochemistry when chiral alcohols are utilized. The original process employed carboxylic acids **1** (or carboxylates **1a**) as the nucleophile producing ester or lactone products[2a] but has since been extended considerably to include a variety of both heteroatom and carbon-based nucleophiles.[2,5] The most commonly employed promoters for this reaction are dialkyl azodicarboxylates, such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD), used in conjunction with triphenylphosphine. New reagents, such as the (cyanomethyl)-trialkylphosphoranes,[6,7] have been developed which also result in inversion of stereochemistry on esterification of chiral alcohols.[6a] These new phosphoranes have also be employed in carbon−carbon[5,7b] and amination[7a] reactions with alcohols.

SCHEME 1. Mechanisms for the Mitsunobu Esterification Reaction



The initial step of the DIAD/triphenylphosphine mediated esterification reaction[3,4] is understood to involve nucleophilic addition of triphenylphosphine to the azodicarboxylate followed by proton transfer from a carboxylic acid to give **3** (Scheme 1). The subsequent steps involve nucleophilic attack of the alcohol **2** on **3** to form an activated alkoxyphosphonium salt **4**[2a] (Scheme 1, Path 1). Finally, S_N2-type displacement by the carboxylate anion on **4** with loss of triphenylphosphine oxide produces the ester with inversion of stereochemistry. Evidence for the existence of an alternative pathway for this reaction proceeding via an acyloxyphosphonium salt (such as **5**, Scheme 1) has been described by Jenkins[8a] and Kunz.[8b] More recently, DeShong[3b,9] demonstrated clear evidence for the involvement of an acyloxyphosphonium salt when hindered alcohols are involved and a further example of a Mitsunobu macrolactonization likely proceeding via the acyloxyphosphonium ion has also recently been described by Smith.[10] In these cases, lactone products were obtained exclusively with retention of stereochemistry. The competitive pathway leading to retention of stereochemistry with hindered alcohols via the acyloxyphosphonium ion **5** is outlined in Scheme 1, Path 2. This scheme also illustrates a competing view of the Mitsunobu reaction involving initial reaction along Path 2. The formation of the basic hydrazide anion leads to subsequent alkoxide formation and "crossover" to the alkoxyphosphonium salt **4**,[3b,11] perhaps proceeding via a mixed alkoxy/acyloxy phosphorane-type intermediate,[4g,8a,12] ultimately yielding the ester with inversion of configuration as the normal outcome. The formation of a basic anion capable of alkoxide formation during the Mitsunobu processes

* Corresponding author.
† Brock University.
‡ Cytec Canada Inc.

(1) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.
(2) For comprehensive reviews see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.
(3) (a) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487. (b) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751.
(4) For further mechanistic discussions see: (a) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org Chem.* **1987**, *52*, 4235. (b) Camp, D. D.; Jenkins, I. D. *Aust. J. Chem.* **1988**, *41*, 1835. (c) Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257. (d) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, 54, 3045. (e) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, 59, 234. (f) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127. (g) Adam, W.; Narita, N.; Nishizawa, Y. *J. Am. Chem. Soc.* **1984**, *106*, 1843.
(5) Ito, S.; Tsunoda, T. *Pure Appl. Chem.* **1999**, *71*, 1053.
(6) (a) Tsunoda, T.; Ozaki, F.; Ito, S. *Tetrahedron Lett.* **1994**, *35*, 5081. (b) Uemoto, K.; Kawahito, A.; Matsushita, N.; Sakamoto, I.; Kaku, H.; Tsunoda, T. *Tetrahedron Lett.* **2001**, *42*, 905.
(7) (a) Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **2001**, *66*, 2518. (b) Zaragoza, F. *J. Org. Chem.* **2002**, *67*, 4963.
(8) (a) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3049. (b) Kunz, H.; Schmidt, P. *Chem. Ber.* **1979**, *112*, 3886.
(9) Ahn, C.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1754.
(10) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102.
(11) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967.
(12) Harvey, P. J.; von Itzstein, M.; Jenkins, I. D. *Tetrahedron* **1997**, *53*, 3933.

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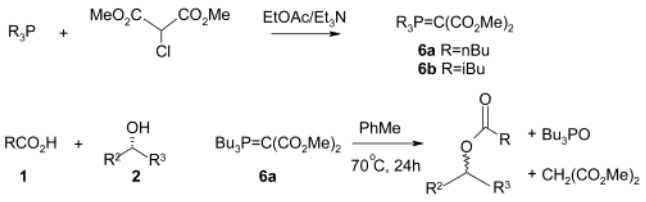
SCHEME 2. Synthesis of Phosphoranes 6 and General Esterification Reaction



described makes it difficult to differentiate between the direct reaction along Path 1 or initial reaction along Path 2 followed by the crossover leading to the necessary alkoxyphosphonium salt **4**.

We have developed a new class of trialkylphosphorane reagent designed to allow for esterification under mild conditions that also helps delineate the competitive pathways described above. These reagents, exemplified by dimethylmalonyltributylphosphorane **6a** (DMTP), are readily prepared by the reaction of a trialkyl phosphine with α-chlorodimethylmalonate in the presence of Et_3N, Scheme 2.

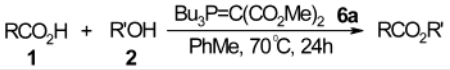
The tributylphosphorane **6a** is a colorless, viscous oil stable under argon at room temperature for at least six months. When exposed to air, the oil slowly solidifies over a period of several days yielding the products of its hydrolysis, tributylphosphine oxide and dimethylmalonate (DMM). The DMTP reagent has been shown to effect the general condensation reaction of a wide variety of carboxylic acids **1** with simple alcohols **2** (Scheme 2) efficiently at neutral pH. The reactions were conducted in dry toluene under argon providing the ester product along with tributylphosphine oxide and DMM. Representative results are summarized in Table 1.

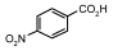
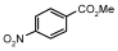
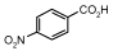
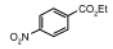
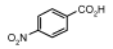
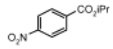
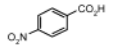
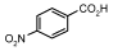
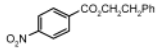
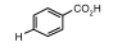
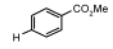
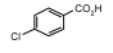
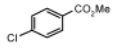
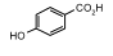
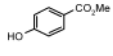
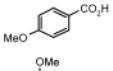
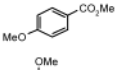
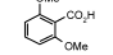
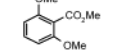
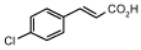
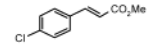
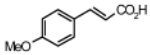
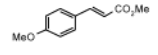
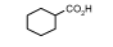
Yields are high with methanol and drop slightly as the bulk of the alcohol increases (Table 1, entries 1−3) while no reaction occurred with the tertiary alcohol *tert*-butanol (Table 1, entry 4). The *β*-aryl alcohol 2-phenyl-1-propanol reacted cleanly without styrene formation (Table, entry 5), indicating that *β*-elimination does not occur. Electron-deficient benzoic acids gave slightly better yields (Table 1, entries 1 and 7) with the same alcohol (compare to entries 6 and 8−10). The reaction may also be carried out successfully in the presence of a free phenol (Table 1, entry 8). Finally, cinnamic and aliphatic acids appear to react without difficulty (Table 1, entries 11−13).

A clear advantage gained when using DMTP is that the side products tributylphosphine oxide and DMM can be largely removed by aqueous base partition (0.2 M Na_2CO_3) thereby simplifying purification. The yields reported in Table 1 pertain to the isolated mass of the purified esters obtained by silica gel chromatography.

The stereochemical implications of the reaction were then investigated utilizing chiral alcohols L-menthol **7**, the secondary aliphatic (*2S*)-hexanol **8**, and the benzylic (1*R*)-1-phenyl-1-propanol **9** under a variety of conditions. The reaction could be carried out successfully in toluene, THF, 1,2-dichloroethane, ethyl acetate, or DMF, however, we determined that toluene and DMF gave slightly higher yields and often complementary results in terms of inversion and retention ratios. The overall results are summarized in Table 2. The reaction of L-menthol **7** with 4-nitrobenzoic acid promoted by phosphorane **6a** in

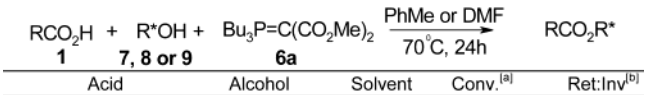
TABLE 1. Esterification Reactions Promoted by Phosphorane 6a

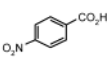
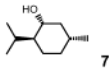
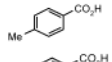
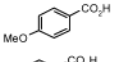
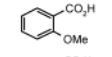
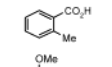
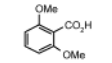
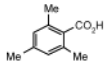
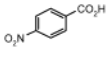
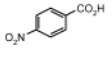
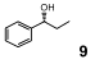
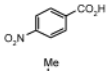
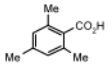
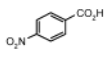
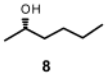
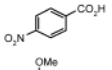
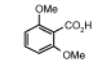
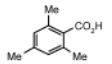


	Acid	Alcohol	Ester	Yield
1		CH_3OH		94%
2		CH_3CH_2OH		86%
3		$(CH_3)_2CHOH$		83%
4		$(CH_3)_3COH$		N.R.
5		$PhCH_2CH_2OH$		88%
6		CH_3OH		70%
7		CH_3OH		98%
8		CH_3OH		75%
9		CH_3OH		75%
10		CH_3OH		77%
11		CH_3OH		70%
12		CH_3OH		81%
13		CH_3CH_2OH		78%

toluene provided the ester with 95% retention of configuration (Table 2, entry 1). The degree of inversion increased as the electron donating ability of the 4-substituent increased (Table 2, entries 1−3) while conversion was higher when electron-deficient 4-substituted benzoic acids were employed. We next investigated the steric nature of the acid with remarkable results. Even a single ortho substituent was seen to have a considerable effect on the outcome of the reaction now delivering the product of inversion with high selectivity (Table 2, entries 4−7). The conversions were lower when mono-ortho-substituted benzoic acids were employed due to competitive formation of the acid anhydride. The reaction of L-menthol with 2,4,6-trimethylbenzoic acid promoted by **6a** gave the ester with greater than 99.5% inversion (Table 2, entry 7). When we returned to the use of 4-nitrobenzoic acid, but performed the reaction in DMF, the ester was obtained in good yield but with 99.2% retention (Table 2, entry 8) in sharp contrast with entry 7. The general results observed with L-menthol were shown to also hold for the other chiral alcohols investigated. Thus, (1*R*)-1-phenyl-1-propanol **9** reacted slowly in DMF with 4-nitrobenzoic acid in the presence of **6a** to give the ester with 64% retention and 36% inversion of configuration at the alcohol center (Table 2, entry 9) while bulky phosphorane **6b** provided 95% retention (Table 2, entry 10). The same reaction conducted in toluene and employing 2,4,6-trimethylbenzoic acid proceeded faster and delivered the ester with 95% inversion of configuration (Table 2, entry 11).

TABLE 2. Esterification Reactions Promoted by Phosphorane 6a



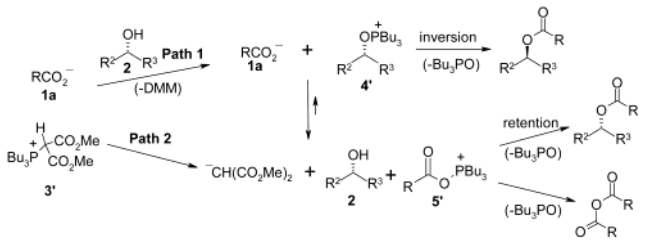
	Acid	Alcohol	Solvent	Conv.[a]	Ret:Inv[b]
1		 **7**	PhMe	82	95:5
2		**7**	PhMe	53	63:37
3		**7**	PhMe	52	33:67
4		**7**	PhMe	28	2:98
5		**7**	PhMe	27	5:95
6		**7**	PhMe	56	4:96
7		**7**	PhMe	78	<0.5:>99.5
8		**7**	DMF	76	99.2:0.8
9		 **9**	DMF	61	64:36
10		**9**	DMF	27[c]	95:5
11		**9**	PhMe	83	5:95
12		 **8**	DMF	71	80:20
13		**8**	DMF	34[c]	97.0:3.0
14		**8**	PhMe	85	<0.1:>99.9
15		**8**	PhMe	84	<0.1:>99.9

[a] Conversions are unoptimized results based on the isolated mass of purified ester after the standard 24 h reaction period. [b] Retention:inversion ratios measured by ^{1}H NMR (menthol) and chiral GC or HPLC in comparison with authentic standards.

Similarly, (2*S*)-2-hexanol **8** could be esterified yielding the products of inversion or retention in a controlled fashion (Table 2, entries 12−15). The reaction in DMF using the tributylphosphorane **6a** and 4-nitrobenzoic acid for the esterification of nonhindered alcohols **8** and **9** gave ester with 80% retention maximum, while bulky triisobutyl phosphorane **6b** gave up to 97% retention (Table 2, entries 10 and 13) although the reaction conversion was lower than when **6a** was employed.

Overall, the product of inversion is favored with use of phosphorane **6a** when the reaction is performed in toluene, using a carboxylic acid with one or more ortho-substituents and preferably these being electron releasing groups (i.e. 2,4,6-trimethyl- or 2,6-dimethoxybenzoic acid). The product of retention is favored when the reaction is performed in DMF with 4-nitrobenzoic acid and is increased as the steric bulk of the trialkyl substituents on the phosphorane increases. In most cases, DMTP **6a** was the reagent of choice in effecting rapid esterification. Interestingly, the triphenylphosphine-derived analogue of **6** was not very effective in promoting the esterification reaction.

SCHEME 3. Postulated Mechanisms for the Esterification with 6a



The mechanistic underpinnings of the reaction were then investigated. In control experiments we determined that alcohols do not enter into reaction with DMPT **6a** in the absence of any carboxylic acid or proton source. However, carboxylic acids react slowly with **6a** in the absence of alcohol to produce the acid anhydride. The reaction of 2,4,6-trimethylbenzoic acid with **6a** (1:1 molar ratio) conducted at 70 °C in $CDCl_3$ was followed by ^{1}H NMR. After 4 h the anhydride was formed in over 90% yield. Isolation of the anhydride in the absence of an alcohol[13] and formation of the ester with retention of configuration[3b,9] are strongly indicative of the intermediacy of an acyloxyphosphonium ion. We also determined that chiral alcohols do not react with the anhydride that is formed under the conditions of the esterification reaction, indicating that products of retention do not arise by simple alcohol acylation; clearly two competing pathways leading to the products of inversion or retention are operative.

To explain the results obtained in our studies, the mechanism outlined in Scheme 3 is postulated. Initial protonation of **6a** provides the activated intermediate **3′**, analogous to **3**, Scheme 1. However, since esters with retention of stereochemistry are formed as well as anhydride in certain cases, the major reaction appears to follow Path 2, proceeding via the acyloxyphosphonium ion intermediate **5′**. In contrast to hydrazide ion formation in the Mitsunobu reaction[3b] the only basic anions that can be formed in the above process are the dimethylmalonyl anion (DMM pK_a approximately 10) or the carboxylate anion, formed by proton transfer to DMM. Under these circumstances, base-mediated crossover to Path 1 (**5′** to **4′**) becomes less favorable and a higher degree of retention is expected.

The substituent effect on the reaction *conversion* with 4-substituted benzoic acids (Table 2, entries 1−3) indicates that 4-nitrobenzoic acid forms the acyloxyphosphonium salt (corresponding to **5′**, Scheme 3) with **6a** faster likely due to its greater acidity. High degrees of retention were also observed with the electron-deficient acids. For more electron-rich carboxylic acids (Table 2, entries 2 and 3) the corresponding carboxylate ions are expected to be stronger bases compared to the 4-nitrobenzoate anion. This would lead to increasing conversion of **5′** to **4′** allowing for higher degrees of inversion as the acid becomes more electron rich.

(13) Greenbaum, M. A.; Denney, D. B.; Hoffman, A. K. *J. Am. Chem. Soc.* **1956**, *78*, 2563.

In addition to the importance of the basicity of the reaction media, steric factors on the alcohol, carboxylic acid, and phosphorane, as well as solvent, play important roles on the balance between the competing pathways leading to retention or inversion. In the case involving the 4-nitrobenzoate anion and a hindered alcohol such as menthol, the crossover path is less likely and the reaction proceeds with high retention (99%) in DMF (Table 2, entry 8) and 95% in toluene (Table 2, entry 1). For 4-nitrobenzoic acid and less hindered alcohols **8** and **9** intermediate ratios of retention and inversion are observed (Table 2, entries 9 and 12). As the steric nature of the acid is increased (Table 2, entries 4−7, 11, 14, and 15) the acyloxyphosphonium salt **5′** becomes more hindered and the attack of alcohol on the acyl center becomes slower allowing more alkoxyphosphonium ion **4′** formation leading to higher degrees of inversion and essentially complete inversion when 2,4,6-trimethylbenzoic acid is used (Table 2, entries 7, 11, and 15).

In the cases where the hindered phosphorane **6b** (Table 2, entries 10 and 13) was employed in conjunction with a nonhindered acid, alkoxide or alcohol attack on the acyl carbon (as opposed to phosphorus) of the acyloxyphosphonium salt **5′** is expected to become dominant, resulting in higher degrees of retention.

Further evidence in accord with the postulated mechanism, including base-mediated crossover, was obtained from the following experiments. The independent generation and trapping of acyloxyphosphonium ions can be accomplished oxidatively through the treatment of a tertiary phosphine with benzoyl peroxide.[13] Thus, a solution of benzoyl peroxide (BPO) in THF was added dropwise to a mixture of L-menthol and tributylphosphine,[13] under our standard esterification conditions (70 °C), and separately with added diisopropylamine. The menthyl ester of benzoic acid was formed in good yield in both cases with retention:inversion ratios of 80:20 and 40:60. This first result is very similar to that obtained with phosphorane **6a** and benzoic acid (ratio 81:19). This provides strong evidence for the acyloxyphosphonium[3b] intermediate **5′** and that Path 1 in Scheme 3 may not be operative under our conditions. The result with diisopropylamine is direct independent evidence for the base-mediated competitive crossover path in the esterification reaction promoted by phosphorane **6a** leading to more inversion. The use of triphenylphosphine and BPO was recently shown to generate anhydrides via the acyloxyphosphonium ion even when the reaction was performed in ethanol as solvent.[3b] Only traces of ethyl ester were produced in this process. In contrast to these results, the tri*alkyl*acyloxyphosphonium ion allows esterification to proceed efficiently even when a stoichiometric amount of a hindered alcohol is present.

In conclusion, we have prepared a new class of trialkylphosphorane that promotes the esterification reaction of chiral alcohols allowing controlled inversion or retention of stereochemistry in a predictable manner. The reagents also promote the esterification of achiral substrates with a wide range of carboxylic acid and alcohol partners under neutral conditions. The major advantage of these new reagents is the controlled levels of inversion or retention that can be achieved through choice of reagents and solvent. These results appear to be manifest because no strongly basic species is generated during the reaction allowing clean separation of the two competing pathways available for the reaction. The side products of this reaction, DMM and tributylphosphine oxide, are largely removed by using a basic extraction protocol, simplifying purification. Strong evidence in favor of the reaction proceeding via an acyloxyphosphonium salt has been uncovered in accord with the mechanism proposed. The question of inversion vs retention in the esterification reaction of chiral alcohols promoted by phosphorane **6a** is rationalized as competition between direct alcohol acylation by the acyloxyphosphonium ion **5′**, leading to retention, and base-mediated crossover from **5′** to the alkoxyphosphonium ion **4′**, resulting in the product of inversion. The implications of these results for the current view of the standard Mitsunobu esterification are such that the basic hydrazide anion may indeed play a very significant role.[3b,11] Basic anions are also implicated during the esterification reaction carried out with (cyanomethyl)trialkylphosphoranes, such as the elimination of the anion of acetonitrile,[6,7] resulting in inversion of stereochemistry also. By analogy with our results, such basic species may provide a crossover path, via alkoxide anion formation, from an initial acyloxyphosphonium salt to an alkoxyphosphonium salt leading ultimately to esters with inversion of stereochemistry. The results described with the new phosphoranes **6a** and **6b**, along with the recent reports by DeShong[9] and Smith,[10] concerning standard Mitsunobu reagents providing esters (lactones) with retention of stereochemistry draw attention to the fine line between the divergent mechanisms operative in the reaction. While inversion of stereochemistry is the normal outcome for the standard Mitsunobu reaction on chiral secondary alcohols, this should no longer be assumed to be the case, particularly in cases where hindered secondary alcohols are involved. A detailed study concerning the independent generation and trapping of acyloxyphosphonium ions is in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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