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Stereoselective Carbon–Carbon Bond Formation via the Mitsunobu Displacement of Chiral Secondary Benzylic Alcohols

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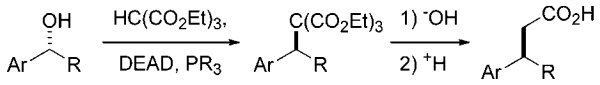
ABSTRACT



The stereoselective displacement of a variety of chiral benzylic alcohols with triethylmethanetricarboxylate (TEMT) under Mitsunobu conditions (DEAD, PMe_3) has been demonstrated to proceed in good yield (70–94%) and with a high degree of inversion. Subsequent saponification and decarboxylation of the products thus obtained provide chiral 3-aryl-3-substituted propanoic acids without racemization.

There are a number of practical methods for the stereoselective synthesis of 3,3-disubstituted propanoic acids (Figure 1). The 1,4-addition of organometallics into chiral α,β-unsaturated esters and amides, for example, has been demonstrated to provide product in high chemical and diastereomeric purity.[1,2] This same reaction has been accomplished in an enantioselective fashion with a variety of nucleophiles and chiral catalysts or promoters.[3,4] Alternatively, the asymmetric hydrogenation[5] of prochiral 3,3-substituted propenoic acids is an effective method for the construction of these moieties. In light of the general occurrence of this class of compounds, we became interested in alternative routes to these intermediates. Specifically, we were intrigued by the idea of a direct S_N2 displacement of an activated chiral alcohol with an enolate equivalent to form a carbon−carbon bond (Figure 1) with inversion of the carbinol stereocenter.

A survey of the literature revealed relatively few methods for the displacement of activated alcohols by carbon nucleophiles in stereoselective fashion. In one case, Reed and coworkers have shown that chiral alcohols derived from cyclic sugars can be displaced with diethyl malonate in high diastereoselectivity after activation with TMSOTf.[6] Researchers from Pfizer have demonstrated that a chiral benzylic mesylate can undergo inversion when treated with a higher

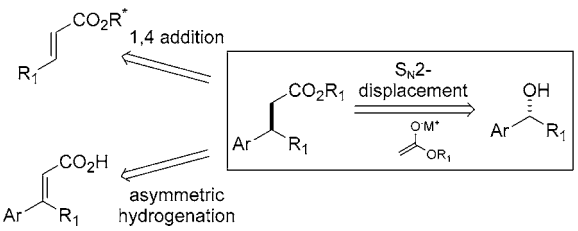


Figure 1. Approaches to 3-aryl-3-substituted propanoic acids.

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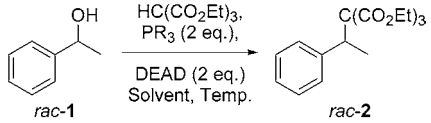
order phenyl cuprate to provide product in good yield and with moderate (ca. 4−10%) loss in enantiomeric purity.[7] Another interesting and often exploited approach involves various modifications of the Mitsunobu reaction.[8] In 1972, Mitsunobu and co-workers showed that (*R*)-2-octanol could be displaced with ethyl cyanoacetate using triphenylphosphine (PPh_3) and diethylazodicarboxylate (DEAD), though product was isolated in low yield and with poor enantiomeric purity.[9] Much additional work has been carried out since involving low pK_a carbon acids and/or specialized activating reagents with a variety of substrates, both racemic[10] and chiral.[11] One particularly interesting example was established by Palmisano and Cravotto wherein triethylmethanetricarboxylate (TEMT), PPh_3, and DEAD were used to displace a diverse array of racemic aliphatic and benzylic alcohols.[12] A single chiral substrate was investigated in this work wherein (*S*)-ethyl lactate was subjected to S_N2-displacement to give product in moderate yield and good enantioselectivity (87% ee).[13] Due to the simplicity of the reaction conditions and ease with which the triester products undergo decarboxylation,[10b,f] we wanted to examine this reaction in more detail with other chiral substrates.

Initially, *racemic* 2-phenyl ethanol **1** was chosen for exploration and reaction optimization (Table 1). Using the original conditions of Palmisano and co-workers, a mixture of the alcohol **1** (1 equiv), TEMT (1.5−2.0 equiv), and PPh_3 (2 equiv) in Et_2O at 0 °C was treated with DEAD[14] (2 equiv) followed by warming to room temperature to give the triester adduct **2** in 40−42% assay yield.[15] The use of a less polar solvent such as toluene was not effective at all, nor was the replacement of PPh_3 with the more bulky tricyclohexylphosphine (PCy_3). However, when tributylphosphine (PBu_3) was used, product was obtained in 70% yield at room temperature

Table 1. Optimization of the Mitsunobu Displacement

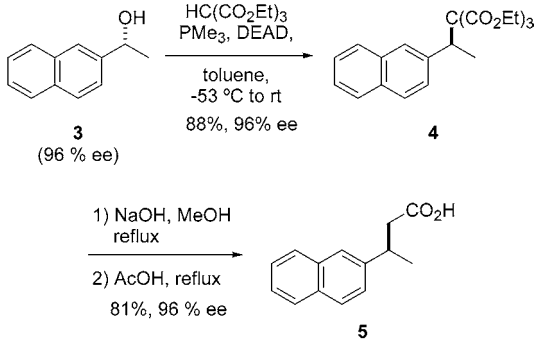


entry	*T*, °C	nucl equiv	PR_3	solvent	yield, %
1	0 to rt	1.5	PPh_3	Et_2O	42
2	0 to rt	2	PPh_3	Et_2O	40
3	rt	2	PPh_3	toluene	12
4	rt	2	PCy_3	toluene	0
5	rt	2	PBu_3	toluene	70
6	−78 to rt	2	PBu_3	toluene	72
7	−78 to rt	2	PEt_3	toluene	73
8	−78 to rt	2	PMe_3	toluene/THF	85
9	−78 to rt	2	PMe_3	THF	75
10	−78 to rt	1.5	PMe_3	THF	49

and 72% yield at −78 °C to rt. A less sterically crowded phosphine, triethyl phosphine (PEt_3), did not enhance conversion, but trimethyl phosphine (PMe_3) was found to be particularly effective, giving **2** in 85% yield (entry 8) in a mixture of THF/toluene (1:1) at low temperature. The use of THF alone led to a slight decrease in yield (75%), and the conversion suffered (49%) when only 1.5 equiv of the nucleophile was employed (entry 10).

With a reasonable set of reaction conditions in hand, a chiral substrate, (*R*)-α-methyl-2-naphthalenemethanol (**3**), was examined to determine the stereoselectivity of this transformation (Scheme 1). Reaction of the alcohol **3** in THF/

Scheme 1



toluene (1:1) at −78 °C gave the triester adduct **4** in 84% yield and 93% ee, indicating that a slight amount of racemization had occurred.[16] In THF alone, product was recovered in significantly lower yield (36%) but in the same optical purity (93% ee). On the other hand, using toluene as solvent at −53 °C to rt, **4** was isolated in *88% yield and 96% ee*; thus, no loss in optical purity was observed during the reaction. The displacement could even be carried out at 0 °C in a mixture of toluene:THF (4:1) to give **4** in 96% ee,

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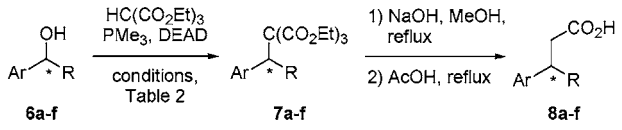
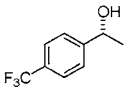
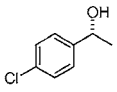
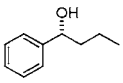
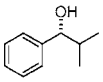
(13) The enantioselectivity of this reaction was determined by derivatization, and comparison of optical rotation to that of a known intermediate.
(14) The activator diisopropylazodicarboxylate (DIAD) was found to be approximately equivalent in this reaction manifold.
(15) Assay yields were determined via quantitative HPLC analysis by comparison to a known amount of pure standard.
(16) See the Supporting Information for methods of ee determination.

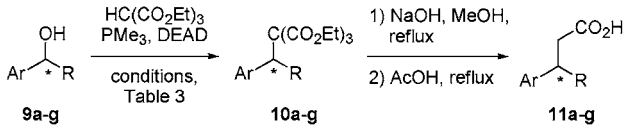
Table 2. General Scope of the Methodology[a]

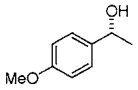
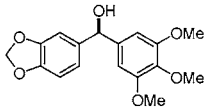
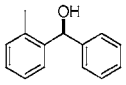
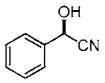
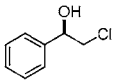


alcohol-**6**		tricarboxylate-**7**		acid-**8**	
substrate	ee, %	yield, %	ee, %	yield, %	ee, %
 **a**	99	A: 82 B: 58 C: 66	- - -	74 85 87	90 99 99
 **b**	99	A: 94	-	84	99
 **c**	99	A: 74	-	90	99
 **d**	99	A: 52 B: 9	- -	55 -	95 -
 **e**	98	A: nr	-	-	-
 **f**	99	A: 82 B: 78	87 99	72 74	87 99
 **g**	99	A: 82	-	84	93

[a] Conditions: (A) THF/toluene (1:1), −78 °C to rt; (B) toluene, −53 °C to rt; (C) toluene, 0 °C to rt.

Table 3. Limitations of the Methodology[a]



alcohol-**9**		tricarboxylate-**10**		acid-**11**	
substrate	ee, %	yield, %	ee, %	yield, %	ee, %
 **a**	99	A: 77 B: 90	- -	89 94	60 54
 **b**	93	A: 63	0	58	-
 **c**	97	A: 70 B: 60	- -	90 90	40 60
 **d**	99	A: 0	-	-	-
 **e**	99	A: 0	-	-	-
 **f**	-	A: <2%	-	-	-
 **g**	-	A: <2%	-	-	-

[a] Conditions: (A) THF/toluene (1:1), −78 °C to rt; (B) toluene, −53 °C to rt.

though the conversion was lower (77%). Subsequent saponification of the triester **4** (96% ee) with NaOH and decarboxylation of the resultant tris-acid gave **5** in 81% isolated yield and with *no erosion in enantiomeric purity* (96% ee).

Having demonstrated the feasibility of this methodology, a number of other chiral substrates were examined (Table 2). The enantiomeric excess of the initial triethylester adducts were not obtained in most cases, rather these intermediates were carried on to the corresponding 3,3-disubstituted propanoic acid products.[17] For example, starting from (*R*)-1-phenylethanol (**6a**, 99% ee), **8a** was isolated in 90% ee and 61% overall yield after displacement (conditions A), saponification, and decarboxylation. Using the same three-step sequence **6b**,**c** gave the corresponding acids **8b**,**c** in *enantiomerically pure form* (>99% ee). Cyclic substrates such as (*S*)-1-indanol **6f** and (*R*)-1-tetrahydronaphthol **6g** also behaved well under these conditions. On the other hand, the displacement of sterically hindered substrates was not as effective. For example, (*R*)-1-phenyl-1-butanol **6d** gave the triester adduct **7d** in a moderate yield (52%) while **6e** did not react at all. However, **7d** could be converted to the acid **8d** in 55% yield and 95% ee after decarboxylation.[18]

During these studies, a significant solvent effect was noticed. For example, the displacement of **6a** in toluene at −53 or 0 °C followed by saponification/decarboxylation gave the acid **8a** in a much improved 99% ee, though in lower overall yield (49−57%). A similar trend was observed with indanol (**6f**) wherein Mitsunobu displacement in toluene gave **7f** in 99% ee versus 87% ee in THF/toluene (conditions A). On the other hand, the inversion of (*R*)-1-phenyl-1-butanol **6d** in toluene led to a much lower yield of the triester adduct **7d** (9%), perhaps due to poor substrate solubility.

A number of benzylic, biaryl, and aliphatic alcohol substrates were also examined using this methodology (Table 3). For example, (*S*)-1-(4-methoxyphenyl)ethanol **9a** gave

(17) In most cases, the triester adducts obtained after alkylation were very poor substrates for analysis by chiral chromatography methods (i.e., SFC, GC, or HPLC).

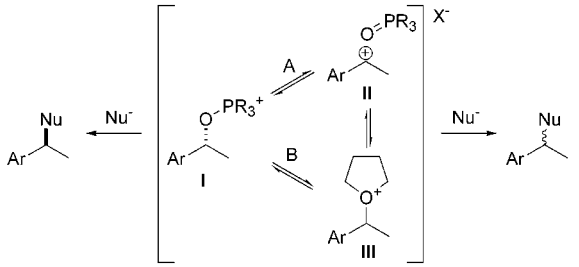


Figure 2. Possible modes of racemization.

the acid **11a** in 69% overall yield and 60% ee after the three-step sequence. The electron-rich biaryl alcohol **9b** gave the corresponding triester adduct **10b** in 63% isolated yield but in *racemic* form. Similarly, 2-methyl-(*S*)-benzyhydrol **9c** could be converted to the acid **11c** in good yield (70%) but poor enantiomeric purity (40% ee) after the three-step sequence. However, when toluene was used during the alkylation step of **9c** the ee of **11c** increased to 60%. Commercially available cyanohydrin **9d** and 1-phenyl-2-chloroethanol **9e** led to extensive decomposition and did not give desired product under these conditions.[18] Nonbenzylic and secondary aliphatic substrates 3-pentanol **9f** and cyclopentanol **9g** reacted in very low yield (<2%).

Clearly, a number of chiral benzylic alcohols (Table 2) undergo stereoselective Mitsunobu-type displacement with triethylmethanetricarboxylate in the presence of DEAD and PMe_3. In some cases racemization is observed, in particular with electron-rich substrates. This erosion in optical purity might be explained by the generally accepted mechanism for the Mitsunobu reaction, which suggests that $ROPR_3^+$ **I** (Figure 2) is a possible reaction intermediate.[19] This species can ionize via an S_N1-type pathway (**II**, pathway A) prior to reaction with the nucleophile or may react with THF (pathway B) to give **III** as has been proposed by Cabaret and co-workers.[11b] The use of toluene seems to dramatically reduce the amount of racemization in some cases (**6a**,**f** and **9c**), possibly via destabilization of these ionization pathways. However, electron-rich substrates such as **9a**−**c** are particularly susceptible, as the corresponding acids **11a**−**c** were obtained in much lower enantiomeric purity compared to that of starting material. As such, it is reasonable to assume that the ionization pathways A or B are stabilized by substrates with electron donating substituents and that changing solvent cannot prevent this. Brown[20] and van der Gen[21] have observed a similar trend in their study of the Mitsunobu reaction of *p*-methoxy substituted benzylic alcohols with carboxylic acid nucleophiles.

In conclusion, we have demonstrated that the Mitsunobu reaction is an effective method for the stereoselective formation of carbon−carbon bonds. The most important features of this methodology are as follows: (1) the use of commercially available triethylmethanetricarboxylate (TEMT) as the carbon acid nucleophile and (2) the use of the trialkyl phosphine PMe_3 along with DEAD to effect the desired transformation. Neutral or electron-poor substrates can be alkylated with a high degree of inversion (Table 2), whereas electron-rich and biaryl systems (**9a**−**c**) undergo significant racemization (Table 3). In some cases, the extent of the erosion in optical purity can be mitigated through the use of toluene. Crowded and aliphatic substrates where found not to be particularly reactive while some benzylic species (**9d**,**e**) led to extensive decomposition. Finally, saponification and decarboxylation of the alkylated triester intermediates gives the corresponding acids without loss of enantiomeric purity, thus representing a viable route to chiral 3-aryl-3-substituted propanoic acids. We are continuing to explore this reaction in more complex systems.

Acknowledgment. We thank Mirlinda Biba and Jimmy Dasilva for the development of chiral assays and Dr. J. Chris McWilliams for the preparation of **6b**,**c** and **9a**.

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

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(18) Significant amounts of either elimination and/or DEAD incorporation were observed.

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