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Chiral Mitsunobu reactions with (1*S*)-(+)-ketopinic acid: kinetic resolutions of secondary alcohols

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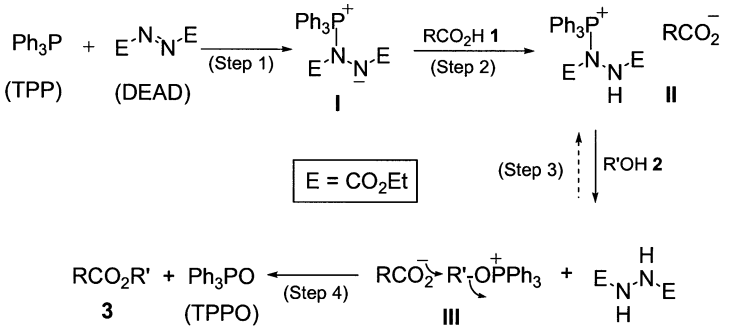
Abstract—Several secondary alcohols undergo the Mitsunobu reaction with triphenylphosphine, diethyl azodicarboxylate and (1*S*)-(+)-ketopinic acid (0.5 equiv. each relative to alcohol) in CH_2Cl_2 solution at −23°C, to furnish the chiral secondary alcohol and its ketopinate ester (d.e. >95%). Chromatographic separation of these and subsequent hydrolysis of the ketopinate ester (KOH/EtOH/0°C) provides the chiral secondary alcohol in overall yields of ~75% and e.e. of ~80%. When the above Mitsunobu reaction is performed with 1 equiv. of all the reactants, an effective dynamic kinetic resolution of the alcohol is observed in two cases, the ketopinate esters being isolated in 63 and 75% yields and >95% d.e. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The resolution of a racemate[1] followed by the inversion of chirality of one of the enantiomers is a general strategy of considerable interest as it may convert all of the racemate into one enantiomeric form. An attractive and intriguing variant of the above strategy is one that would combine the resolution and inversion steps into a single operation, as would obtain, for instance, when a kinetic resolution[2] can be performed with concomitant inversion of chirality. We report herein the design of a chiral version of the Mitsunobu reaction, thereby demonstrating the above ideas within the class of secondary alcohol possessing a single stereogenic centre.

The Mitsunobu reaction is perhaps the most favoured method for the inversion of secondary alcohols.[3–5] It involves the reaction of the alcohol **2** (Scheme 1) with a mixture of triphenylphosphine (TPP), diethyl azodicarboxylate (DEAD) and a carboxylic acid **1**, (RCO_2H). The reaction is believed to occur via the initial nucleophilic addition of TPP to DEAD to afford the betaine **I** (step 1); this is protonated by the carboxylic acid **1** to afford the azaphosphonium carboxylate **II** (step 2), the overall formation of **II** being irreversible. Nucleophilic attack at the tetracoordinate phosphorus atom of **II** by the alcohol **2** (step 3), results in a species formally considered to be **III** (an activated derivative of **2**), which suffers nucleophilic attack by the carboxylate anion (of **1**). The resulting inverted ester **3** is accompa-



Scheme 1.

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nied by triphenylphosphine oxide (TPPO) (step 4), the formation of which is the thermodynamic driving force for the overall reaction.

The design of a chiral version of the above process is an interesting exercise: among the many possibilities those involving chiral phosphines, chiral azodicarboxylate and chiral carboxylic acid as auxiliaries are obvious. Also, possible enantioselection in Scheme 1 may in principle be expected to occur at either of the steps 3 or 4 or both (which involve both the chiral auxiliary and the alcohol), with the conditions and caveats discussed below. (Note also that the slow step in the Mitsunobu reaction is believed to be step 4; however, the enantioselection may in principle occur in any step, as long as there is no effective racemisation in a further step.)

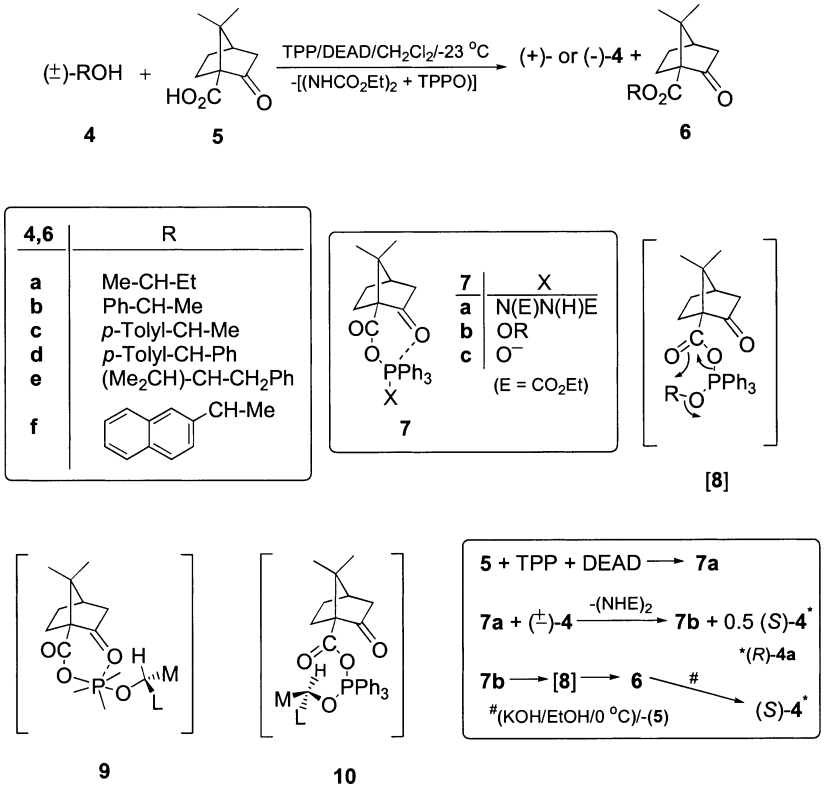
Enantioselection only at step 4 would require step 3 to be reversible (shown by a dotted arrow), which would allow the 'wrong' alcohol enantiomer to dissociate and be deactivated. (Otherwise both enantiomers would be inverted, although at different rates: an essentially null result.) There is apparently no evidence for the reversibility of step 3, but it cannot be ruled out: the equilibrium constant would be largely determined by the relative stability of a cationic phosphorus centre that is bound to an alkoxy oxygen atom or a hydrazinyl-carbamate nitrogen atom, and is not easily predicted. And as any equilibrium is expected to be relatively rapidly attained in view of the ease of nucleophilic substitution at phosphorus, it would allow the required selective dissociation of one of the alcohol enantiomers (mentioned above).

Also, enantioselection at both steps 3 and 4 may or may not be mutually reinforcing. In principle, enantioselection at step 3 is possible with chiral RCO_2H **1**, chiral azodicarboxylate or chiral phosphine, whereas that at step 4 is possible only with chiral RCO_2H **1** or chiral phosphine (azodicarboxylate not being involved). Enantioselection with chiral RCO_2H **1** at step 3 may arise from the (known) deprotonation of the alcohol **2** by the carboxylate anion, as also by its proximity (as counterion) to the cationic phosphorus atom (the site of selectivity).

The first chiral Mitsunobu reaction was reported by Kellogg and co-workers,[6] who employed two chiral dioxaphosphepanes with a range of alcohols and acids. Although the overall enantiospecificity was apparently moderate ($\leq 39\%$), the unreacted alcohols could be obtained in high e.e.s at less than complete conversion. (This seems to be due to an equimolar amount of the chiral phosphepane having been employed—half a molar equivalent being ideal for an efficient kinetic resolution—although a competitive racemisation of the chiral ester formed was also suspected.) We are not aware of any further reports of chiral Mitsunobu reactions.

2. Mitsunobu reactions with (1*S*)-ketopinic acid

The present work was motivated by the fact that chiral RCO_2H is perhaps the simplest of the possible choices as auxiliary, and the availability of (1*S*)-(+)-ketopinic acid in hand. The secondary alcohols (**4**, Scheme 2)



Scheme 2.

listed in Table 1 were treated with TPP, DEAD and (1*S*)-(+)-ketopinic acid **5** (0.5 equiv. each) in dichloromethane solution at −23°C. Upon the usual work-up, the reaction mixture was found to be a 1:1 mixture of the starting alcohol **4** and its ketopinate ester **6** (by IR and NMR), thus indicating that the expected Mitsunobu reaction had occurred.

In the NMR of the above mixture, three sets of multiplet signals may in principle be expected, one set for the unreacted alcohol enantiomer **4** and two sets for the diastereomeric esters **6**. Multiplet signals observed in the δ 4.3–6.2 region were thus attributed to the tertiary *OCH* protons in **4** (δ 4.3–5.3) and **6** (δ 5.0–6.2). Interestingly, the lower field signals of the esters **6** generally showed only one of the sets, indicating total enantioselectivity within the limits of NMR detection.

Column chromatographic resolution of the above reaction mixture afforded the enantiomerically enriched alcohol **4** and the diastereomeric mixture of ketopinate esters **6**, generally in ~80% yields. The specific rotations of the alcohols **4** were thus determined and compared with reported values to obtain the enantiomeric excesses (generally ~90%). Unfortunately, the esters **6** epimerised partially (~15%) during the above chromatography, as seen by the appearance of an additional set of *OCH* proton signals ($\Delta\delta$ ~0.15) in the NMR spectrum. (In fact, this supports the above conclusion that the enantioselectivity in the reaction is generally total, as it is seen that the diastereomers are distinguishable.)

The ketopinates **6** were hydrolysed in ethanolic potassium hydroxide at 0°C and the resulting alcohols **4** and ketopinic acid **5** were thus recovered: the specific rotations indicated that in each case the alcohol was identical to the unreacted alcohol recovered chromatographically above, and despite the above epimerisation of **6**, the e.e. values were generally ~75%. The overall yields of the alcohol **4** (combined after the hydrolysis) are also ~75%, the weighted average enantiomeric excess being generally in the range 78–86%.

Higher reaction temperatures led to a reduction in the stereoselectivity of the above reactions: at room temperature, the esters **6a** and **6b** were formed in 16 and 72% d.e., respectively (the hydrolysis of **6** overwhelmingly via acyl-oxygen cleavage is indicated above; all the above yields are based on a theoretical maximum yield for recovered **4** and **6** of 50% each).

3. Dynamic kinetic resolution

In another set of experiments, the racemic alcohols **4** were treated with 1 molar equivalent of the Mitsunobu reagent (derived from Ph_3P+DEAD+**5**) in CH_2Cl_2 at 25°C. Interestingly, it was observed that two of the ketopinates, **6d** and **6f**, were obtained in yields higher than expected (63–75%, expected ≤50%) and with complete diastereoselectivity as shown by NMR (see in Table 1 under yields of **6** in parentheses; these yields were determined in the reaction mixture by NMR against a *p*-dinitrobenzene internal standard, in view of

Table 1. Kinetic resolution of the racemate alcohols (±)-**4** with 1*S*-(+)-ketopinic acid (**5**; Scheme 2): percent yields, e.e.s (for **4**) and d.e.s (for **6**)[18]

Alcohol: (±)-**4**	Resolved alcohol: (+)- or (−)-**4**							Ester: **6**[d]		
	Unreacted[a]		Saponified[b]		Combined[c]					
	Yield	E.e.	Yield	E.e.	Yield	E.e.	*R*/*S*-(+/−)	Yield[e]	(*R*/*S*)[f]	D.e.
a		70		–			*R*-(−)[g]	42	(*R*)	>95
b	44	90	34	77	78	84	*S*-(−)[h]	37	(*S*)	87
c	38	82	37	73	75	78	*S*-(−)[i]	41	(*S*)	76
d	44	90	38	82	82	86	*S*-(−)[j]	41 (63)	(*S*)	>95
e	40	–	33	–	73	–	*S*-(−)[k]	42	(*S*)	>95
f	40	90	38	79	78	85	*S*-(−)[l]	40 (75)	(*S*)	78

[a] Refers to the enantiomer left unreacted in the Mitsunobu reaction (theoretical maximum yield = 50%).
[b] Obtained by hydrolysis of the ester **6** formed in the Mitsunobu reaction (theoretical maximum yield = 50%).
[c] The e.e. values are weighted averages of the unreacted and saponified samples.
[d] Purified by chromatography.
[e] The numbers in parenthesis refer to the yields of the ester in the dynamic kinetic resolutions, observed in the Mitsunobu reaction between equimolar amounts of all the reactants (by NMR against *p*-dinitrobenzene as internal standard, the d.e.s in these two cases being total by NMR).
[f] The configurations pertain to the alkoxy carbon atom and are based on those of the hydrolysed alcohol (except in the case of **4a**).
[g] Ref. 12 (rotations were determined on the crude aqueous extract after the Mitsunobu reaction, **6a** not being saponified).
[h] Ref. 13.
[i] Ref. 14.
[j] Ref. 15.
[k] Ref. 16; the e.e.s of **4e** (unreacted and saponified) were exceptionally low (~20%): the near total d.e. of the corresponding ester **6e** suggests that **4e** is unstable towards the conditions employed—chromatography and base treatment.
[l] Ref. 17.

the instability of **6** to chromatography). The simplest explanation for the formation of one diastereomer in >50% yield in the above process, appears to be a dynamic kinetic resolution process:[7,8] in this the enantiomers of a derivative of the alcohol **4** along the reaction path are equilibrated, stereoselective reaction of one of these with the chiral acid **6** then displacing the equilibrium. The intermediate that is best positioned along the reaction path, and most likely to be so equilibrated, is the activated derivative corresponding to **III** (Scheme 1), presumably via dissociation to a carbocation or the corresponding ion pair (discussed below).

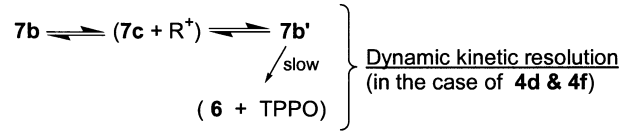
No dynamic kinetic resolution was observed in the other cases under the above 'equimolar conditions', the corresponding diastereomeric esters being generally formed in equal amounts by NMR. It seems very likely that the stability of the derived benzylic cations is the origin of the phenomenon, based on the relatively extended conjugation possible in the cations derived from **4d** and **4f**.

4. Mechanism of enantioselection

It would appear that the generally high e.e. values obtained indicate a rigid transition state, whether at step 3 or at step 4 (Scheme 1). In the event that enantioselectivity originates at step 3, a carboxylate anion relatively tightly bound to the cationic phosphorus atom—perhaps making it pentavalent—is indicated. (There is indeed P^{31} NMR evidence for such intermediates.[3]) It is, in fact, likely that rigid intermediates such as **7** are involved, in which a pentavalent phosphorus atom is also coordinated with the ketone oxygen atom; **7a** and **7b** are analogous to **II** and **III** (Scheme 1), respectively (hexacoordinate phosphorus is known[9,10]). The rigidity of the tricyclic framework of **7a** would confer high stereoselectivity to its reaction with the alcohol **4** to yield **7b**; interestingly, **7b** may then collapse intramolecularly—and hence stereospecifically—to **6** by acyloxy transfer from phosphorus to carbon via the six-membered cyclic transition state designated as [**8**]. (This 6-*endo*-tet process,[11] would be allowed by the presence of the second row phosphorus atom. It is assumed above that the selectivity originates in step 3, Scheme 1, but see below.)

It can be seen in Table 1 that the (*S*)-alcohols generally remain unreacted in the above Mitsunobu process (except in the case of 2-butanol **4a**), a tentative explanation being as follows. In the event that the stereoselection occurs at step 3 (Scheme 1), the preferential formation of the diastereomer of **7b** from the (*R*)-alcohol (i.e. **9**) is possible. (A square bipyramidal structure at phosphorus in **9** with the two most electronegative groups, the acyloxy and the alkoxy, occupying the apical positions is assumed.[9]) In the event that the stereoselection occurs at step 4 (Scheme 1), a transition state such as derived from **10**, i.e. [**8**] incorporating the (*R*)-alcohol is possible. In both **9** and **10** the small group (H) points towards the region of highest steric congestion (the polycyclic framework and the *exo* face of the camphane moiety), the large group (L) points away from this region, and the medium group (M) points towards a region of intermediate steric congestion (the *endo* face of the capmphane moiety). The reasons for the preferential reaction of the (*S*)-isomer in the case of **4a** are not entirely clear at this stage.

The dynamic kinetic resolutions observed in the two cases above could occur via the initial reversible dissociation of **7b** to **7c** leading to the formation of the more stable of the two possible diastereomers (indicated as **7b′**, Scheme 3, corresponding to **9**, Scheme 2), which would slowly collapse to the ester **6** as discussed above.



Scheme 3.

5. Conclusions

A new process of kinetic resolution with concomitant chirality inversion—one of the cherished goals of asymmetric synthesis—has been designed and demonstrated. The process defines a chiral version of the well-known Mitsunobu reaction, employing the readily accessible (1*S*)-(+)-ketopinic acid as a chiral auxiliary, and affords various secondary alcohols in excellent yields and enantiomeric excesses. Two of the benzylic alcohols also undergo dynamic kinetic resolution during the above Mitsunobu reaction, providing relatively high yields of chiral alcohol. The above reactions apparently involve a rigid phosphorane intermediate formed from Ph_3P, the ketopinic acid and the alcohol. Additionally the results also offer some insights into the mechanism of the Mitsunobu reaction itself.

Acknowledgements

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18. **Typical experimental procedure for the Mitsunobu reaction**: The alcohol (±)-**4** (2.0 mmol), ketopinic acid **5** (1.0 mmol) and Ph_3P (1.0 mmol) were dissolved in CH_2Cl_2 (5 mL). The solution was cooled to −23°C and treated with DEAD (1.0 mmol in 5 mL CH_2Cl_2), dropwise with stirring under N_2. DEAD (yellow) was decolourised almost instantaneously, the mixture was allowed to warm to rt (TPPO was crystallised from the mixture by stirring the reaction at <0°C for ~1 h) and worked up by washing with water, drying ($MgSO_4$) and distilling the solvent in vacuo. The residue was chromatographed on SiO_2 (eluent, EtOAc–hexanes) to obtain the pure alcohol **4** (*R* or *S*) and the ketopinate **6**.
Typical experimental procedure for ester hydrolysis: A solution of the ester **6** (0.5 mmol) in 40% KOH in absolute EtOH (5 mL) was stirred at 0°C/12 h. The alcohol (*R* or *S*) was isolated by extraction with CH_2Cl_2, followed by standard extractive workup. (The acid **5** was recovered quantitatively from the aqueous layer.) Products were identified by IR, ^{1}H NMR (300, 400 and 500 MHz) and MS. ν (cm^{-1}): **4** (~3350, OH), **6** (~1750, ester CO; ~1725, keto CO). δ_H as discussed above. Esters **6** were viscous liquids unstable to distillation (*m*/*e*: M^+ observed except for **6a** and **6e**). Polarimetry furnished the $[\alpha]_D$ values for the alcohols **4**, and the e.e.s were calculated from the reported $[\alpha]_D$ values (Refs. 12–17).