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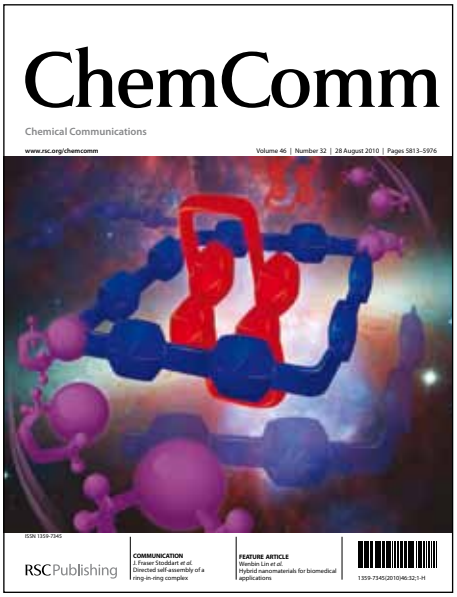

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Novel Preparation of Chiral α-Amino Acids Using the Mitsunobu-Tsunoda reaction

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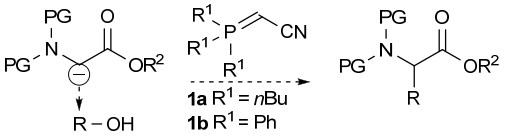
An efficient synthesis of racemic or optically active α-amino acids by modified-Mitsunobu alkylation of a racemic or chiral glycine template from alcohols was developed. Libraries of amino acids were prepared in moderate to good yield with good to high enantioselectivity. This simple method widens the scope for preparation of structurally diverse amino acids.

Enantiopure non-proteinogenic α-amino acids (α-AAs) are of great importance for pharmaceutical development.[1] They are essential for peptide synthesis and are indispensable in total synthesis and ligand elaboration as either chiral building blocks or chiral catalysts.[2] The increasing demand for unnatural α-AAs has encouraged many research groups to focus their effort on the development of novel methods for the rapid synthesis of a large pool of enantiopure non-natural α-AAs.

Classical approaches to access these materials such as resolution of racemic mixtures have quickly given way to the use of more powerful asymmetric synthesis methods.[3] Even though the field of catalytic asymmetric synthesis has witnessed impressive growth,[4] the gold rush for the almighty catalyst so far failed to deliver an inexpensive, readily available and universal catalyst. The necessary screening for the optimum catalyst renders the use of catalytic asymmetric synthesis laborious and restricts its use for the preparation of libraries of compounds. On the other hand, the introduction of the amino acid side-chain using a diastereoselective approach offers access to a wide range of chiral compounds from a single precursor. This is usually achieved *via* the deprotometallation of an appropriate chiral glycine auxiliary followed by reaction with an electrophile.[5] To be attractive, chiral auxiliaries must either be commercially available or readily prepared in a few steps and should be inexpensive or easily recycled. However, the alkylation process often requires strong bases or cryogenic temperatures and to date, only halides and pseudo-halides have been used as the electrophilic partners. In many cases organohalides have limited shelf-lives and are best used immediately after their preparation. These restrictions are considerably limiting the use of the diastereoselective approach for high throughput synthesis.

To the best of our knowledge, the synthesis of α-AAs using alcohols as pro-electrophiles has not been reported. Not only it would save one step compared to using halides, but the vast pool of structurally diverse commercially-available alcohols would afford a significant increase in the number of non-proteinogenic α-AAs that become readily accessible. Such a process is therefore highly desirable for both academic and industrial research.

Although the Mitsunobu reaction constitutes the most commonly used reaction to effect the substitution of alcohols with nucleophiles,[6] it suffers serious limitations. The p*K*a restrictions (nucleophile acidic hydrogen p*K*a ≤11) considerably hamper the scope of nucleophiles which can be used efficiently. Furthermore, difficulties in isolation often arise due to the presence of triphenylphosphine oxide and hydrazine side-products. In this regard considerable progress has been achieved and modified Mitsunobu reagents have been developed.[7] Notably, cyanomethylene tributylphosphorane (CMBP) **1a** and cyanomethylene triphenylphosphorane (CMPP) **1b**, reported by Tsunoda *et al.*[8] are capable of forming C-C bonds by effecting the alkylation of alcohols by nucleophiles with a pK_a <23.



Scheme 1. General strategy for the synthesis of α-AAs by direct Mitsunobu-type alkylation with alcohol electrophiles.

We postulated that glycine derivatives should be suitable nucleophiles to use in conjunction with these novel phosphoranes (Scheme 1). Herein, we report the first Mitsunobu-Tsunoda alkylation of glycine templates with a broad range of alcohols providing α-AAs in both racemic and enantioenriched forms.

Previous work by O'Donnell *et al.*[9] focused on the structure of the glycine templates, demonstrated that protection of the amine functionality as a benzophenone imine was key for the success of the phase-transfer catalyzed alkylation reaction. Not only does the electron-withdrawing effect of the benzophenone Schiff base increase the acidity of the methylene protons (p*K*a ≈ 18.7) but also the steric bulk prevents undesired dialkylation at the α-carbon. Therefore, we decided to use O'Donnell's scaffold for our proposed Mitsunobu-Tsunoda alkylation study.

Initially, we examined the reaction of *N*-(diphenylmethylene) glycine *tert*-butyl ester (**2**) with benzyl alcohol in order to determine the optimum reaction conditions. Given that elimination of acetonitrile is an entropic driving force for the Mitsunobu-Tsunoda alkylation, the reaction was carried out at high temperatures. Our first attempts using CMPP **1b** afforded only trace quantities of the desired product after heating in toluene at 100 °C overnight. Unfortunately, changing the temperature, time, concentration or equivalents of CMPP and alcohol failed to improve the reaction outcome. At this point we decided to investigate the more reactive phosphorane CMBP **1a**. Hence, treatment of **2** with one equivalent of benzyl alcohol and one equivalent of **1a** in toluene (0.5 M) at 100 °C afforded the desired product **3a** in 40% yield. Complete conversion could be achieved by increasing the concentration to 1 M, the reaction temperature to 120 °C and using two equivalents of both the phosphorane and the alcohol. Pleasingly, under these conditions no dialkylation side-product was detected and the desired product **3a** was isolated in an improved 82% yield.

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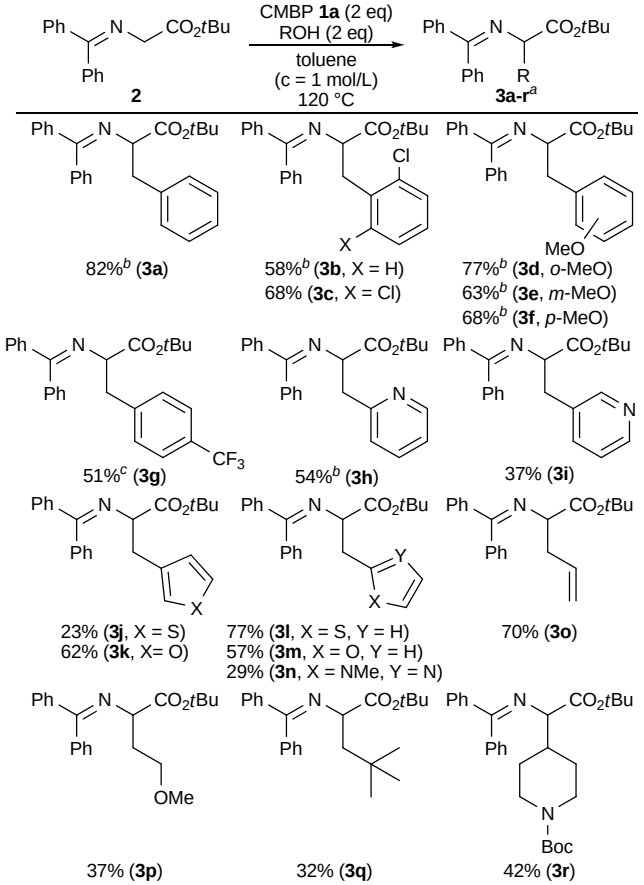

Scheme 2. Scope of the Mitsunobu-Tsunoda alkylation for the racemic synthesis of α-AAs. [a] Yields were determined after semi-preparative HPLC unless otherwise stated. [b] Yields were determined after flash chromatography. [c] Yield was obtained using 3 equivalents of 4-(trifluoromethyl)benzyl alcohol and CMBP.

Encouraged by these promising results we next investigated the scope of the reaction. A broad range of racemic α-AA derivatives were prepared by simply mixing alcohols with *N*-(diphenylmethylene)glycine *tert*-butyl ester **2** and cyano-methylene tributylphosphorane **1a** in toluene and heating to 120 °C in a plain screwed-cap vial. The alkylated products were easily purified from the highly polar tributylphosphine oxide and volatile acetonitrile side-products, providing the α-AA precursors **3a-r** in good to moderate yields (Scheme 2).

Use of di-*ortho* substituted benzyl alcohols afforded substituted phenylalanine analogue **3c** in similar yield to the less hindered 2-chlorophenylalanine **3b**, indicating that the presence of bulky substituents at the *ortho* position of the benzene ring were well-tolerated. The reaction also proceeded smoothly when the electron-withdrawing chlorine atom was replaced with an electron-donating methoxy group providing **3d** in 77% yield. Furthermore, switching the methoxy group to the *meta* or *para* position provided the pure products **3e** and **3f** in good yields (63% and 68%, respectively). Perhaps surprisingly, when an electron-withdrawing group was present in the *para* position such as trifluoromethyl, the alkylation of **2** was found to be sluggish, but **3g** could still be obtained in 51% yield by adding additional equivalents of CMPB and 4-(trifluoromethyl)benzyl alcohol. Heteroaromatic derivatives, which remain mostly prepared by biotechnological means and have so far proven difficult to access by chemical synthesis, were readily prepared from thienyl-, furanyl-, imidazolyl- and pyridyl- methanol in yields ranging from 23-77% (**3h-n**). Furthermore, it was pleasing to observe that both allylic and primary aliphatic alcohols reacted successfully with **2** to form the desired allylglycine **3o**, *O*-methylated homoserine **3p** and homo-*tert*-leucine **3q** in 70%, 37% and 32% yield, respectively. Interestingly, secondary alcohols were also good substrates for the Mitsunobu-Tsunoda alkylation of **2** as exemplified by the reaction of *N*-Boc-4-hydroxypiperidine which afforded product **3r** in 42% yield.

We next focused on the extension of our methodology to the asymmetric desymmetrisation of prochiral glycine equivalents for the synthesis of optically active α-amino acids. Although diastereoselective alkylations most commonly proceed at sub-zero to room temperatures,[5] we were curious to see whether we could control the diastereofacial selectivity in spite of the high reaction temperatures required. We proposed that the nickel complex developed by Belokon,[10] and successfully used by our laboratories and others for the synthesis of non-natural enantiopure amino acids,[11] would provide a suitable template for the Mitsunobu-Tsunoda reaction, as only mild conditions are required to effect its deprotonation. Furthermore, the high diastereoselectivity observed during the alkylation of the Belokon complex using NaOH as a base at room temperature are believed to be the results of a thermodynamically favoured reaction pathway.[10b] It was therefore hoped that the alkylation under Mitsunobu-Tsunoda conditions would also take place under thermodynamic control and lead to the same high diastereo-selectivity despite the elevated temperature required. Additionally, the Ni^{II} complex is easily accessible on a kilogram scale and can be stored for months without degradation. Ni^{II} complex **4** derived from (*S*)-2-[*N*-(*N'*-benzyl-prolyl) amino] benzophenone (BPB) and glycine was prepared in excellent yield in just three steps from inexpensive starting materials.[12]

Gratifyingly, the direct alkylation of Gly-Ni-(*S*)-BPB **4** with various alcohols **5a-h** using CMBP **1a** took place providing the desired products **6a-h** with good yields and good diastereofacial selectivity (Table 1). The diastereoisomeric ratios, determined by ^{1}H NMR analysis, were found to be ≥86:14, and could be increased to 99:1 after separation of the minor (*S*,*R*)-diastereoisomer by column chromatography, except in the case of **6f**, where the diastereoisomers were inseparable. Alkylation with benzyl alcohol (**5a**), substituted benzyl alcohols (**5b-c**), heteroaryl carbinols (**5d-e**) and allyl alcohol (**5f**) gave good yields (59-83%) while unsaturated alcohols such as 5-hexen-1-ol afforded the desired product **6g** in a moderate 46% yield. The addition of an unactivated long alkyl chain that is difficult to attain with standard methods, also proceeded smoothly yielding **6h** in 60% yield.

Removal of the Ni^{II} complex under mild acidic conditions followed by ion-exchange chromatography, afforded the free amino acids **7a-g** in good to excellent yields (67-99%). However, the general procedure could not be applied to the preparation of the lipophilic heptylglycine **7h**, which could not be extracted into the aqueous layer. In this case concentration of the reaction, filtration of the precipitated BPB ligand, then reverse-phase chromatography afforded the pure hydrochloride salt of the

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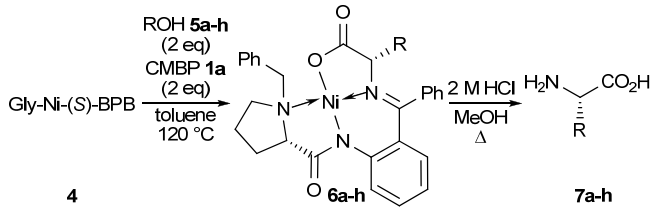
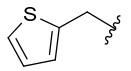
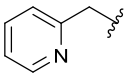
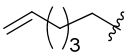
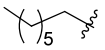
Table 1. Scope of the Mitsunobu-Tsunoda alkylation for the enantioselective synthesis of α-AAs.



Entry	R	Yield[a] % (6)	dr[b]	Yield[c] % (7)	ee[d] %
a	Ph	75	90/10 (99/1)	79	95
b	*o*-MeOC$_6$H$_4$	72	87/13 (99/1)	67	>99
c	*p*-MeOC$_6$H$_4$	59	90/10 (99/1)	87	96
d		68	96/4 (99/1)	79	92
e		83	87/13 (99/1)	quant.	96
f		78	90/10	quant.	81
g		46	89/11 (99/1)	quant.	95
h		60	86/14 (99/1)	64	97

[a] Yields were determined after isolation of the major isomer by flash chromatography. [b] dr were determined by ^{1}H NMR analysis of crude reaction mixtures (dr of the major isomer isolated by flash chromatography). [c] Yields were determined after ion-exchange chromatography. [d] ee were determined by chiral HPLC on Chirobiotic T column.

desired amino acid **7h** in 64% yield. The enantiomeric purities were determined by chiral HPLC, confirming that little to no racemization occurred during the cleavage step. While hydrolysis of the pure (*S*,*S*)-diastereoisomers afforded the amino acids in 92-99% enantiomeric purity (**7a-e**, **7g-h**), cleavage of the diastereoisomeric mixture of **6f** gave the free amino acid **7f** in 81% ee. The BPB ligand was also recovered in quantitative yield by simple extraction with dichloromethane.

In conclusion, we have developed a novel methodology for the synthesis of α-AAs, using readily available alcohol substrates and an inexpensive glycine chiral auxiliary. Thanks to the variety, ready availability and stability of the alcohol electrophilic partners and the facile reaction set-up, this new method allows access to a wide range of novel optically active α-AAs in a simple library-style operating manner. Furthermore, neither cryogenic temperatures nor expensive chiral ligands were necessary to achieve consistently high ee. The methodology reported herein therefore, provides a powerful addition to the armoury of existing methods to effect the synthesis of novel chiral non-proteinogenic α-AAs.

The alkylation of Ni^{II} complexes derived from other α-AAs (for the synthesis of dialkylated α-AAs), is currently under examination. Further investigations into the effect of modifying the Tsunoda reagent are also in progress in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details for the synthesis and characterization data, copies of ^{1}H and ^{13}C NMR and chiral HPLC spectra. See DOI: 10.1039/b000000x/

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