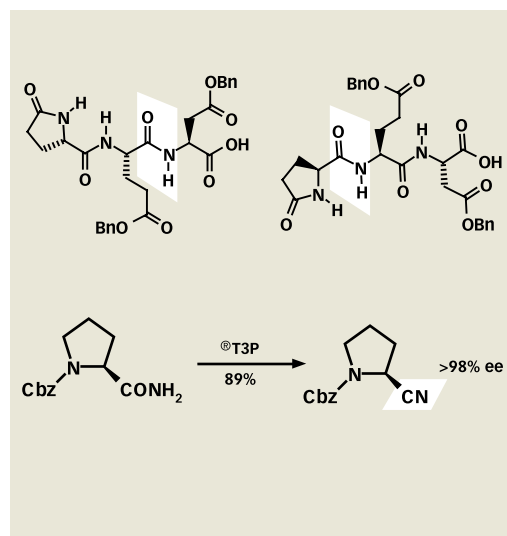


®T3P – Propane Phosphonic Acid Anhydride

The coupling agent of the future

Coupling and water removal are synthesis tools that stand at the cutting edge of high purity and cost effective manufacture of amides and esters for the pharmaceutical and fine chemical industries. At the forefront of this technology is ®T3P, a highly selective coupling agent.

®T3P is an exceptional reagent for amide/peptide bond formation. ®T3P is very easy to use and combines excellent reaction selectivity, low epimerization with high product purities and yields. Because of its properties, hazardous additives such as explosive HOBt, are not required.¹ Additionally, the ®T3P reagent is really “green” – non-toxic, non-allergenic/non-sensitizing, and the salt by-products are non-hazardous and completely water soluble. These salts are readily removed via an aqueous wash at the conclusion of the reaction. ®T3P also works well in other condensation reactions, such as esterifications. In addition, it may be used as a mild reagent for alcohol oxidations and the Lossen rearrangement. A detailed application package is available on request.



®T3P is offered as a 50% solution, or other concentrations, and in a wide variety of solvents dependent on the customer's needs.

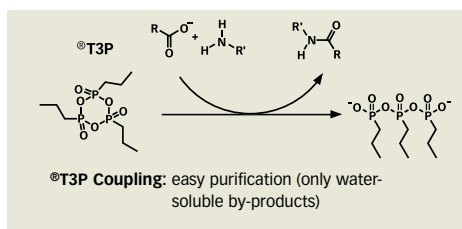
	Purification	Yield	Epimerization	Toxicity	Price/gram	Overall
®T3P	● easy	● high	● low	● low	● medium	● ● ● ● ● ●
EDC (WSC)	● easy	● medium	● medium	● high	● medium	● ● ● ● ● ●
TBTU/HBTU	● difficult	● high	● low	● medium	● medium	● ● ● ● ● ●
PyCloP	● difficult	● high	● low	● medium	● very high	● ● ● ● ● ●
BOP	● difficult	● high	● low	● very high	● high	● ● ● ● ● ●
DCC/HOBt	● very difficult	● medium	● medium	● high	● low	● ● ● ● ● ●
DCC	● very difficult	● low	● high	● high	● low	● ● ● ● ● ●

Recent studies with ®T3P

Whether you are in need of a coupling agent or a water scavenger, ®T3P delivers process efficiencies that lead to more effective use of equipment while providing increased yields for more economical use of raw materials. At the same time ®T3P is non-toxic, non-allergenic, its application is very easy, and it offers high selectivities yielding high-purity products.

Reaction mechanism

®T3P converts the oxygen of the carboxylic acid into a leaving group. The by-product formed by the leaving group can be easily extracted at commercial scale with low costs by use of an aqueous work-up. The yield advantages made possible by high selectivity's and minor product losses through easy purification, makes ®T3P attractive for late stage synthesis steps and especially for production of molecules with multiple chiral centers.



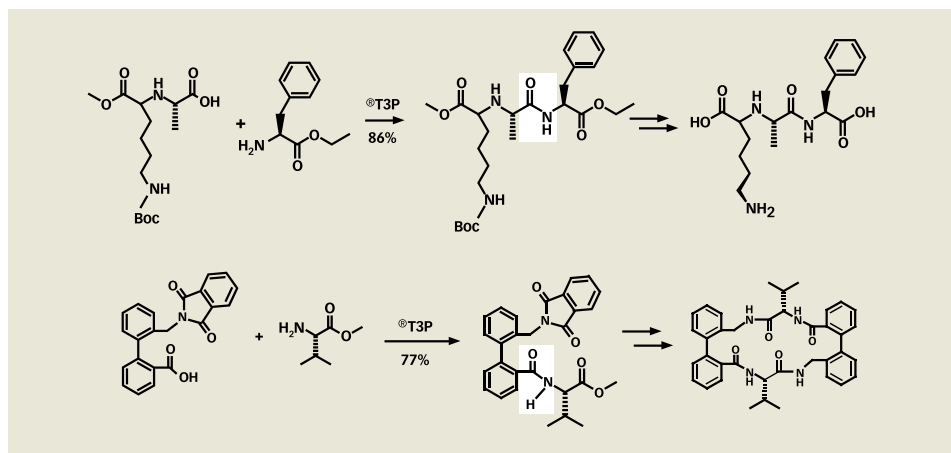
®T3P: coupling performance leader

In performance comparison between ®T3P and other peptide coupling reagents for the preparation of a nonapeptide drug, it was found that ®T3P was superior to other reagents with regards to yield and low epimerization.²

	Yield	Epimerization
®T3P	86.6	1.8
DCC/HOBt*	60.5	5.9
EDC/HOBt*	67.3	11.1
TBTU	53.2	9.1
HBTU	65.6	16.1
PyCloP	4.1	–
PyBOP	63.4	14.2

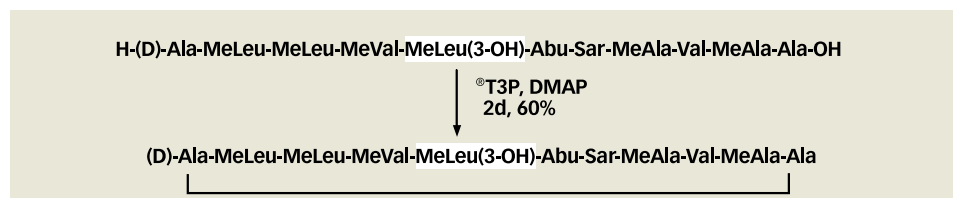
* HOBt has recently been classified as an explosive compound.¹

®T3P as a classical peptide coupling reagent



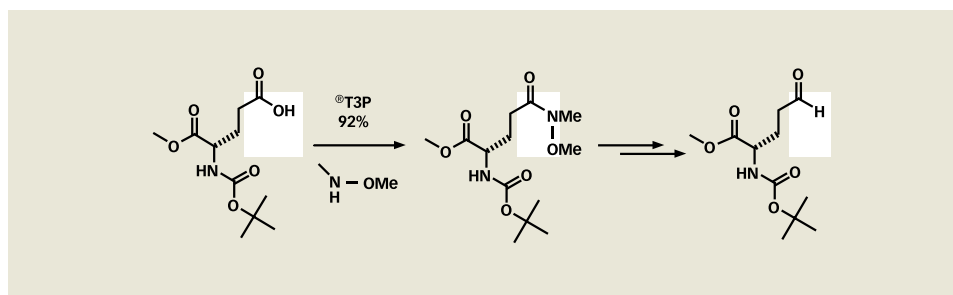
®T3P allows the synthesis of peptide libraries with high yields and low epimerisation resulting in the generation of high throughput screening libraries without the need for costly and time consuming column purification. Due to simple work-up, with complete and easy removal of the by-product of ®T3P this process is ideally tailored for high throughput screening equipment.³

®T3P is the choice in cyclizations



The selectivity of ®T3P allows cyclizations of high-value molecules like cyclosporin derivatives to proceed without additional steps to protect the MeLeu(3-OH) alcohol. This gives high yields which are otherwise unachievable.⁴

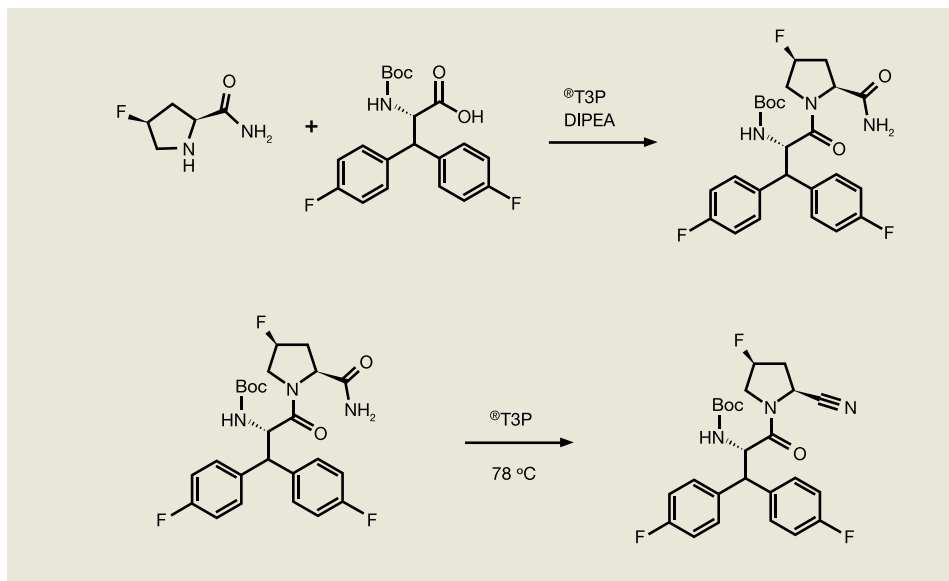
Mild preparation of Weinreb amides



Under mild conditions, ®T3P is the ideal activator for the formation of Weinreb amides. The selectivity of ®T3P results in low levels of epimerization and high yields. These Weinreb amides can be converted into aldehydes in high yield, while the chiral information is fully maintained.⁵

Preparation of Amides and Nitriles

®T3P has been successfully applied in amide bond formation and in nitrile generation in an economic route to Denagliptin (GSK). In this synthesis ®T3P gave superior yields over other alternative syntheses with no epimerisation being observed. ®T3P was found to be extremely cost effective and provided a safe and efficient alternative to the use of HATU previously investigated.⁶



Esters with ®T3P

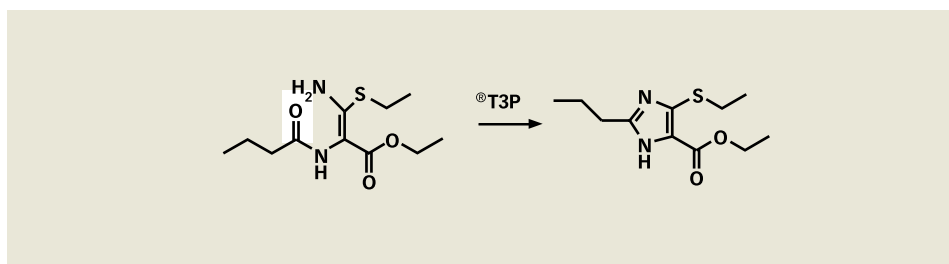
Due to the high selectivity and low epimerization characteristics of ®T3P, this coupling agent is also ideal for the formation of complex and sensitive esters.⁷

C,C coupling reactions

®T3P is used for mild acylation reactions on benzoyl rings and on pharmacophores like pyrazoles. Pyrazoles are frequently found in today's active pharmaceutical ingredients.⁸

Formation of substituted heterocycles water removal combined with acid catalysis

®T3P is a liquid organic equivalent to the highly reactive and hazardous P₂O₅ (phosphorous pentoxide) and PPA (polyphosphoric acid) chemical water removal reagents, as well as an alternative to costly molecular sieves for high-end reactive water removal from liquid media. At the same time, it provides Lewis acid catalysis potential for reactions.⁹



Facts about ®T3P

Molecular weight	318.19 g/mol
Empirical formula	(C ₃ H ₇ O ₂ P) ₃
Assay (³¹ P-NMR %w/w) ®T3P	> 50.0%
Pyropropane phosphonic acid	< 10.0%
Propane phosphonic acid	< 0.5%
Solvent	< 50.0%
Appearance	slightly yellowish liquid
Shelf life	at least 1 year if stored correctly

Specifications

®T3P is currently supplied as a 50% (w/w) solution in a variety of solvents including N,N-dimethylformamide, ethyl acetate, butyl acetate, THF, methyl THF, toluene, methylene chloride or in any other solvent with which it is compatible (e.g. polyethylene glycol ethers).

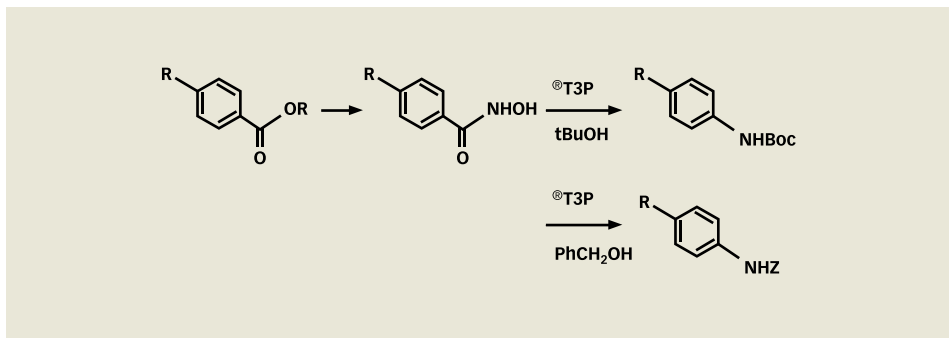
Efficient processing with ®T3P

®T3P often requires only a mixing stage and is available in a variety of solvents, allowing for greater adaptation and optimization to your process needs. High purity products can be isolated easily by hydrolysis and phase separation. This is a result of the ionic nature of the reaction by-products of ®T3P. This removes the need for more expensive chromatographic columns currently used in many processes. Additionally, ®T3P processes result in products with high purity and low epimerisation, allowing a reduction of process and raw material costs.

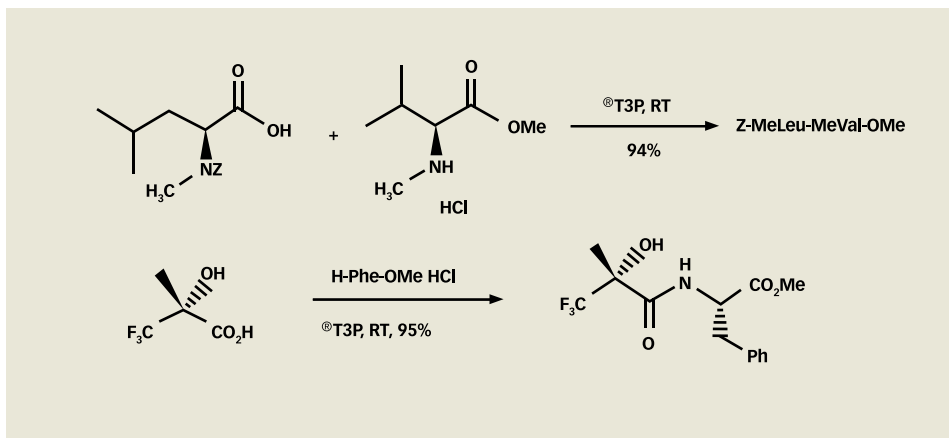
Selective transformations of multifunctional molecules

Research has shown ®T3P to be efficient for highly selective transformations of multi-functional molecules, including:

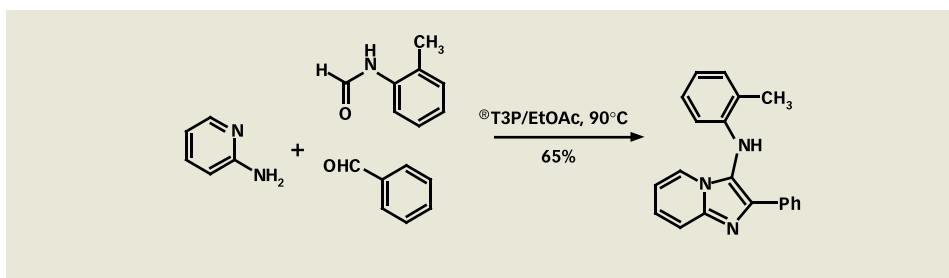
Conversion of esters to N-protected anilines via hydroxamic acids.



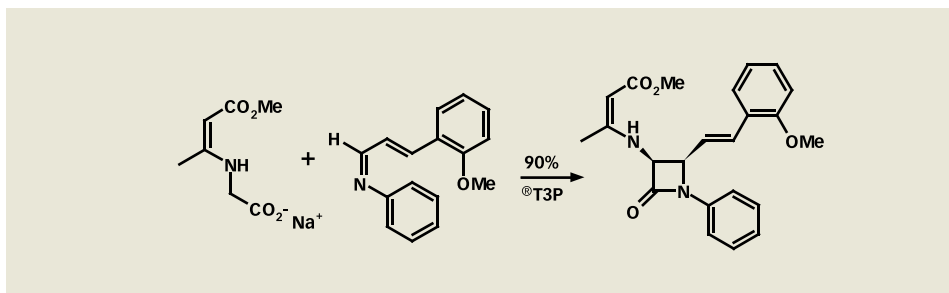
Sterically very hindered amides, where ®T3P is more cost-efficient in use when compared with PyBOP. Significant savings are achieved in reagent costs and at the same time work-up problems and toxicity problems can be avoided.



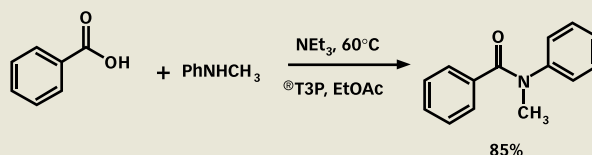
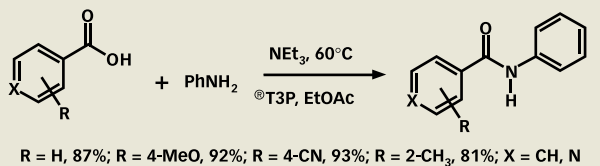
In-situ generation of isonitriles, for construction of complex heterocyclic systems.



Formation of β-lactams, where very mild conditions are needed (0°C), in addition to full stereo control.¹⁰

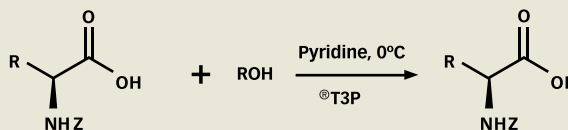


Formation of anilides using free acids to obtain high yields.

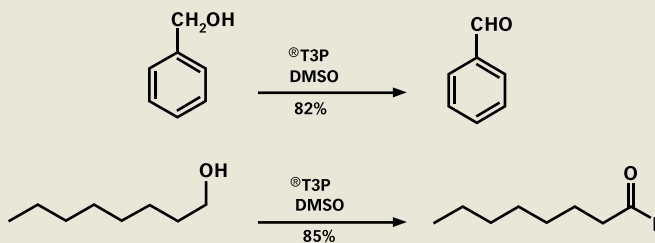


Formation of amino acid esters¹¹, such as:

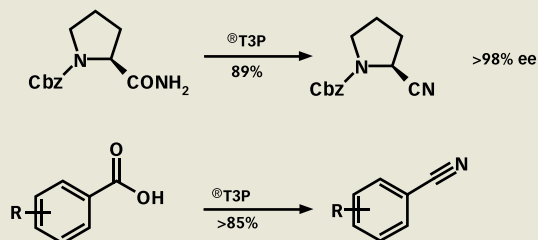
Z-Tyr(tBu)-O-cyclohexyl	91%
Z-Tyr(tBu)-O-n-butyl	78%
Z-Tyr(tBu)-O-n-hexyl	85%
Z-Tyr(tBu)-O-isopropyl	83%
Z-Phe-OtBu	76%
Z-Asp(OtBu)-OEt	79%



Oxidation reactions, with very mild conditions (-50 - $+10^\circ\text{C}$), easy work-up and no heavy metals. The usual problems with the product separation from dicyclohexylurea by-product if DCC is used instead of ®T3P can be avoided.



Conversion of acids to nitriles, with very mild conditions, high yields and easy application. Nitrile formation can be accomplished without interference with almost all other functional groups. A 96% isolated yield has been achieved already at a scale as high as several 100 kg in an example with very complex substitution pattern.



Safety and ease of handling

®T3P is a reagent with low toxicity and low allergenic concern, permitting simple handling and low cost transportation. It also reduces health and environmental risks in scaling processes from the lab to commercial scale. Unlike HOBt, a benzotriazole which is explosive¹, ®T3P is safe to handle at all scales.

The ®T3P process development service

The application of ®T3P is fundamentally different from any other commercially available coupling agent. Archimica has more than 20 years of experience in coupling reactions for a variety of chemical reactants from amides, heterocycles, esters and carbon-carbon bonds to the solid phase synthesis of peptide libraries. This

extensive knowledge base of coupling reactions allows Archimica to provide a free application program for ®T3P process development. With proper optimization support from Archimica, ®T3P has been proven to be a better reagent than others in many cases.

The ®T3P application program is carried out under a confidentiality agreement and allows companies to maintain complete control of their intellectual property. Under the process development service, Archimica's expertise allows integration of the coupling and extraction steps required, and provides an optimum solution for commercial scale-up.

Quality management

®T3P is produced in an ISO9001:2008 certified facility.

Availability

With an annual production capacity of several 100 tonnes and with pilot scale-facilities dedicated to the manufacture of custom ®T3P solutions tailored for specific needs, Archimica offers customers a wide range of solutions.

Notification

Before ®T3P can be released to our customers (even in sample quantities) we require the completion of our end use documentation.

®T3P is a registered trademark of Archimica.

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