EUTICALS
The Pharmaceutical & Fine Chemical Company

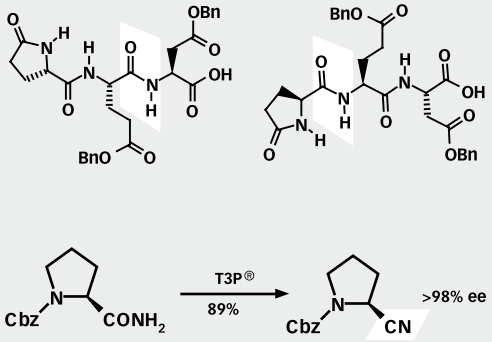
TECHNOLOGY STRENGTHS

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.

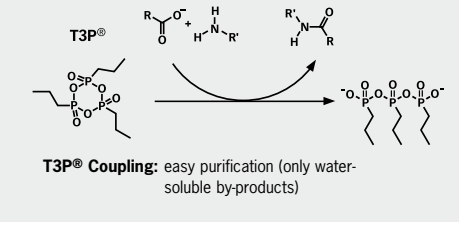
	Purification	Yield	Epimerization	Toxicity	Price/gram	Overall
T3P®	easy	high	low	low	medium	
EDC (WSC)	easy	medium	medium	high	medium	
TBTU/HBTU	difficult	high	low	medium	medium	
PyClоP	difficult	high	low	medium	very high	
BOP	difficult	high	low	very high	high	
DCC/HOBt	very difficult	medium	medium	high	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: easy purification (only water-soluble by-products)

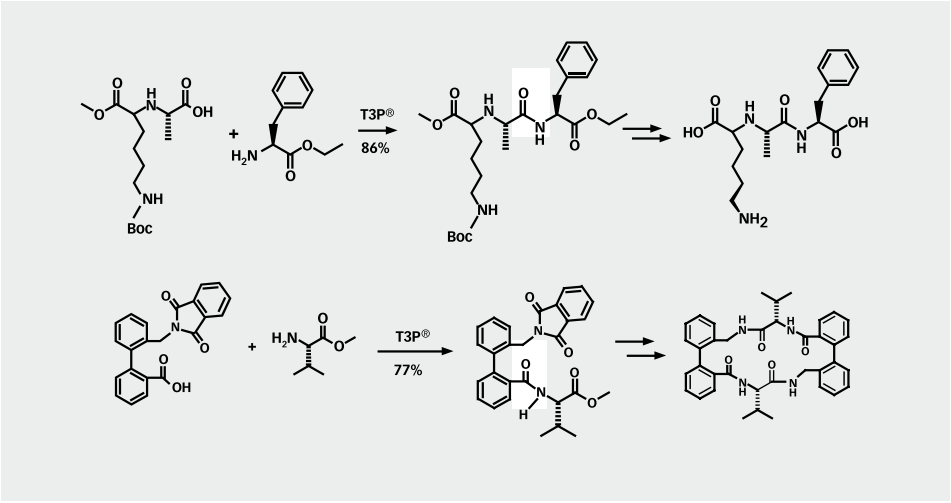
T3P®: coupling performance leader

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

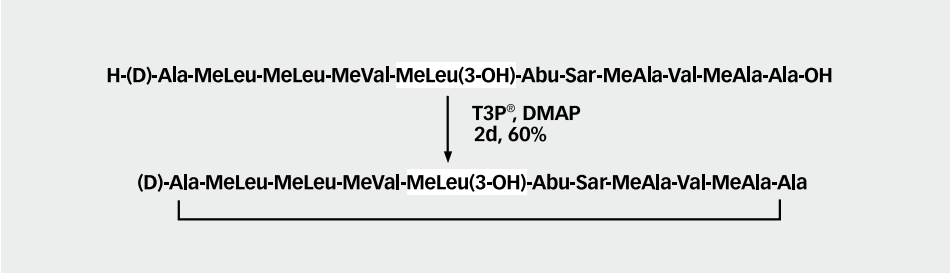
* HOBt has recently been classified as an explosive compound.[1]

T3P® as a classical peptide coupling reagent



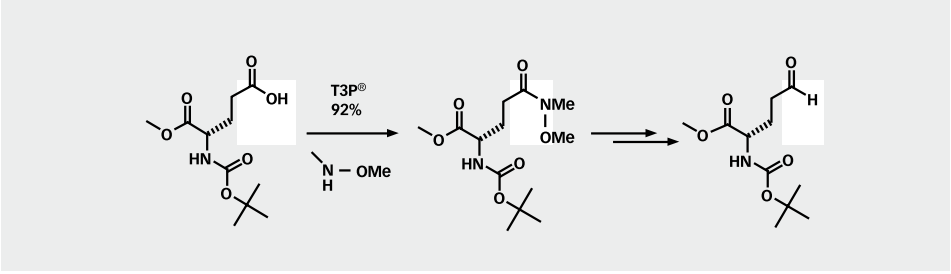
T3P® allows the synthesis of peptide libraries with high yields and low epimerisation resulting in the generation of high throughput screening libraries without the need for costly and time consuming column purification. Due to simple work-up, with complete and easy removal of the by-product of T3P®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

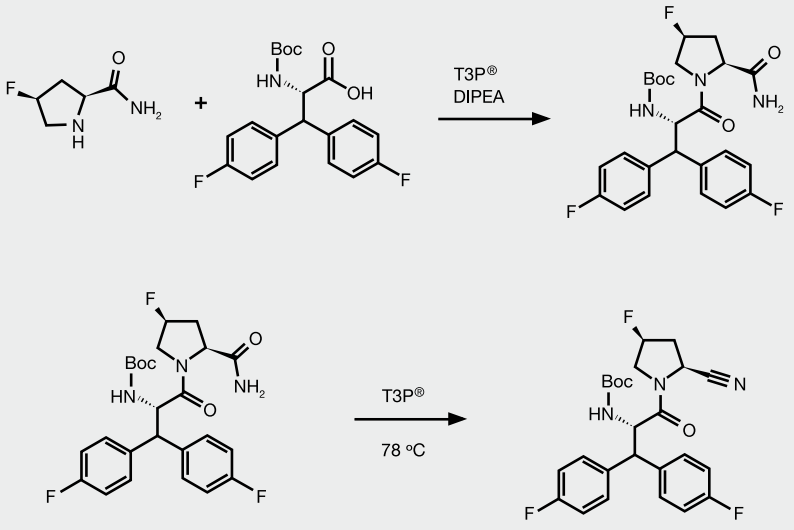
Mild preparation of Weinreb amides



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]

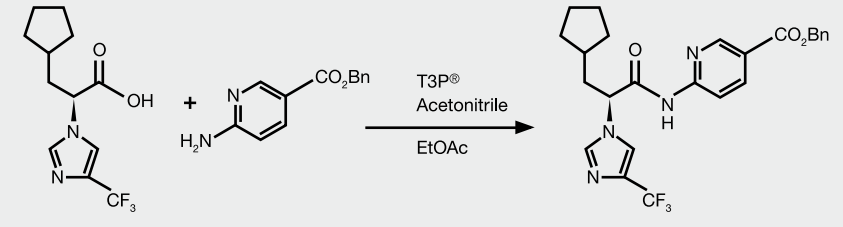
Preparation of Amides and Nitriles

T3P® has been successfully applied in amide bond formation and in nitrile generation in an economic route to Denagliptin (GlaxoSmithKline). 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]



Amide formation with epimerization – prone substrates

With epimerization-prone substrates, T3P® is the coupling reagent of choice. In development of a process for production of multi-kg quantities of a hepatoselective glucokinase activator (Pfizer) in which formation of an amide was the penultimate synthetic step, Dunetz [7, 8] screened a wide range of traditionally used coupling reagents (eg DCC, EDC (with or without HOAt), HATU etc.). T3P® was selected for scale-up after showing that it was clearly superior in giving products with minimal racemization and also being most suitable for scale-up. Further screening of T3P® for amide formation with other other racemization-prone substrates confirmed the general excellent application of T3P® for such reactions.



Facts about T3P®

Molecular weight	**318.19 g/mol**
Empirical formula	**$(C_3H_7O_2P)_3$**
CAS No.	**68957-94-8**
Assay T3P®	**> 50.0%**
Solvent	**< 50.0%**
Appearance	**slightly yellowish liquid**
Shelf life	**at least 1 year if stored correctly**

Available Solvents

T3P® is currently supplied as a 50% (w/w) solution in a variety of solvents allowing for greater adaptation and optimization to your process needs. Solvents include:

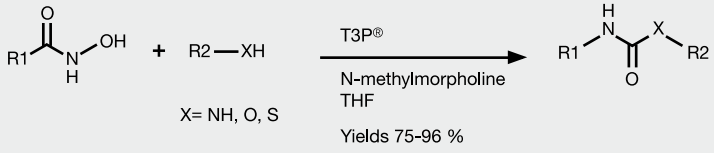
- ethyl acetate
- butyl acetate
- THF
- 2-MeTHF
- toluene
- N,N-dimethylformamide
- chlorobenzene
- methylene chloride
- acetonitrile
- any other compatible solvent

Use of T3P® often requires only a single mixing stage at 0–25 °C. High purity products can be easily isolated by hydrolysis of residual T3P® and phase separation. This is a result of the ionic nature of the reaction by-products of T3P®, and 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 raw material and process costs.

Selective transformations of multifunctional molecules

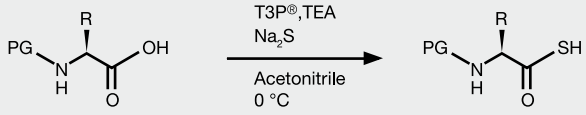
Research has shown T3P® to be efficient for highly selective transformations of multi-functional molecules, including:

Lossen rearrangement. Synthesis of urea and carbamate derivatives.[9]

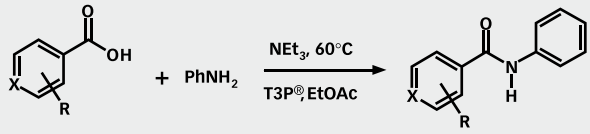


Formation of thioacids from N-protected amino acids and peptides.[10]

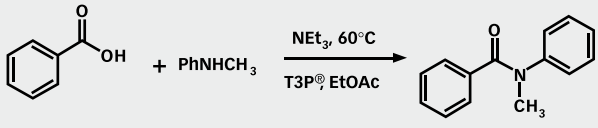
Wide range of amino acids and peptides, including sterically hindered substrates, tested in this transformation giving typical yields of 80-95% with non-detectable levels racemisation. Formed products were readily isolated using mild work-up procedures.



Formation of anilides using free acids to obtain high yields.[15]



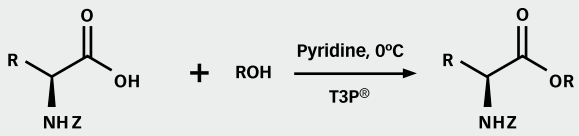
R = H, 87%; R = 4-MeO, 92%; R = 4-CN, 93%; R = 2-CH_3, 81%; X = CH, N



85%

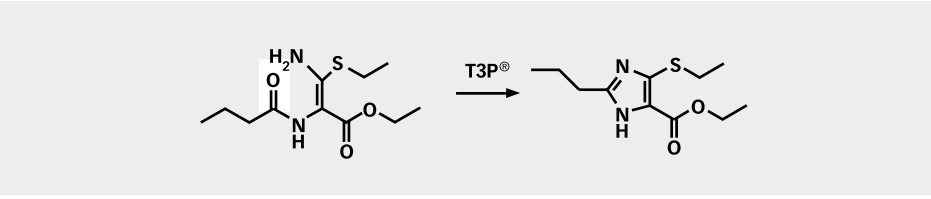
Formation of amino acid esters[11], such as:

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%

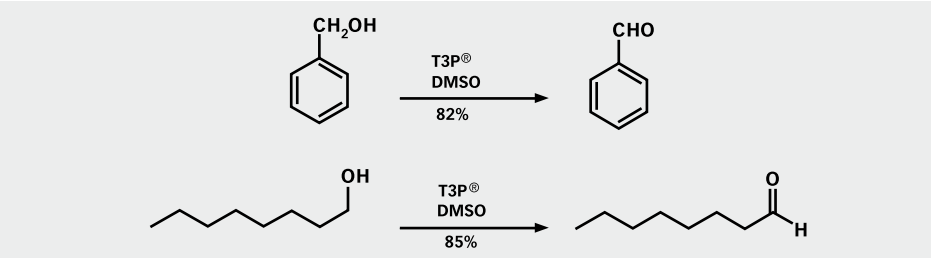


Formation of substituted heterocycles water removal combined with acid catalysis

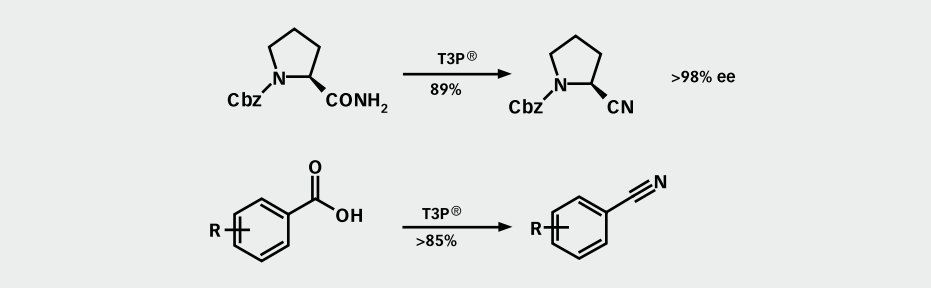
T3P® is a liquid organic equivalent to the highly reactive and hazardous P_2O_5 (phosphorous pentoxide) and PPA (polyphosphoric acid) chemical water removal reagents. At the same time, it provides Lewis acid catalysis potential for reactions.[12]



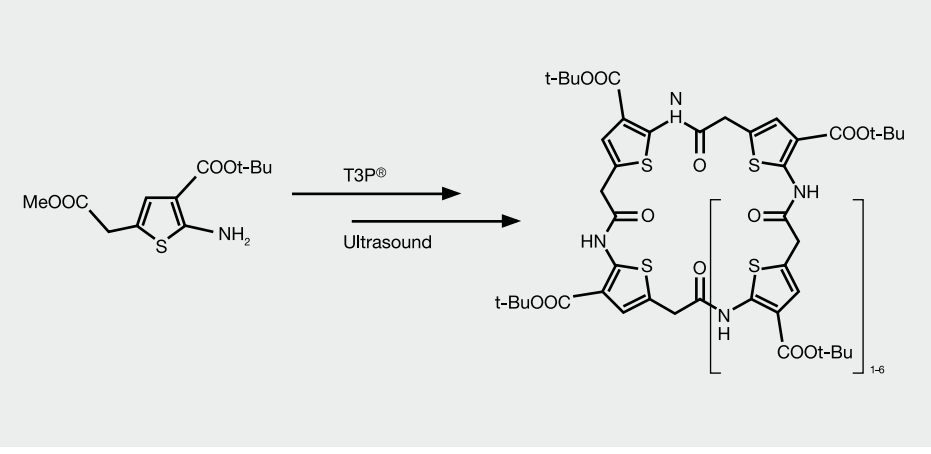
Oxidation reactions, with very mild conditions (0–5 °C), easy work-up and no heavy metals. The usual problems with the product separation from dicyclohexylurea by-product if DCC is used instead of T3P® can be avoided. [15]



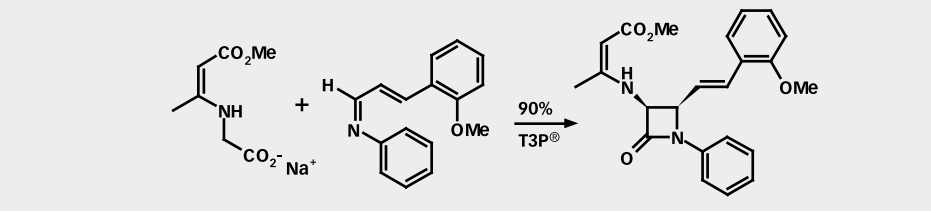
Conversion of acids to nitriles, with very mild conditions, high yields and easy application. Nitrile formation can be accomplished without interference with almost all other functional groups. A 96% isolated yield has been achieved already at a scale as high as several 100 kg in an example with very complex substitution pattern.[15]



Synthesis of linear and cyclic oligoamides having a thiophene backbone has been carried out using T3P®. The combination of an ultrasonic technique to diminish intramolecular backfolding of longer oligoamide chains and T3P® as coupling reagent leads to shorter reaction times and higher yields for both cyclic and linear oligomers.[13]



Formation of ß-lactams, where very mild conditions are needed (0°C), in addition to full stereo control.[14]



Safety and ease of handling

T3P® is a reagent with no 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 explosive[1], 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. Euticals has more than 25 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 Euticals to provide a free application program for T3P® process development. With proper optimization support from Euticals, 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, Euticals' 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, Euticals 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 Euticals.

Bibliography

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