

## ***Coupling Agent®T3P – The Water Scavenger***

High-Performance Amide/Peptide Bond Formations,  
Dehydrations and Condensations





As the usage of high value building blocks, including chiral amides and peptides, continues to increase in the pharmaceutical industry, companies must focus on optimizing the process costs of coupling reactions through **high selectivities and yields** and **low epimerization** – particularly in late stage syntheses. ®T3P (propane phosphonic acid anhydride) is the ideal coupling agent for these needs, delivering outstanding performance at moderate costs with **low toxicity** and **easy work up**.

Short-term Couplings for Long-term Success

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## ®T3P – The Water Scavenger

Compared with other modern coupling agents ®T3P delivers outstanding advantages. ®T3P has low toxicity and produces an easily purified product with high yield and low epimerization.

- Carbodiimides such as DCC are toxic compounds, which give moderate yields and frequently result in high levels of epimerization. Additionally, purification after using DCC is cost intensive.
- Although reagent costs of TBTU/HBTU are comparable to ®T3P, these reagents have two key disadvantages. Both have sensitizing properties and the purification of the resulting products is cost intensive.
- BOP generates high yields and low epimerization, but BOP and its resulting by-products are highly toxic resulting in additional handling costs and safety measures.
- HOBT has recently been classified as explosive.

	<i>Yield</i>	<i>Epimerization</i>
<b>®T3P</b>	86.6	1.8
<b>DCC/HOBT</b>	60.5	5.9
<b>EDC/HOBT</b>	67.3	11.1
<b>TBTU</b>	53.2	9.1
<b>HBTU</b>	65.6	16.1
<b>PyCloP</b>	4.1	–
<b>PyBOP</b>	63.4	14.2

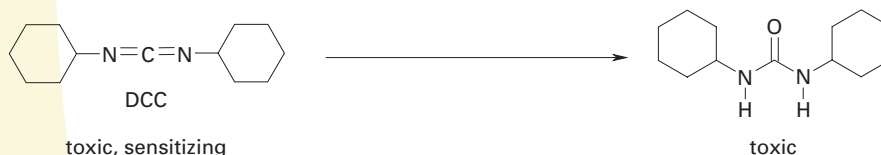
J. Hiebl et al., J. Pept. Res. 1999, 54, 54  
For further details please turn to page 6.

	<i>Purification</i>	<i>Yield</i>	<i>Epimerization</i>	<i>Toxicity</i>	<i>Price/gram</i>	
<b>®T3P</b>	• easy	• high	• low	• low	• medium	•••••
<b>EDC (WSC)</b>	• easy	• medium	• medium	• high	• medium	•••••
<b>TBTU/HBTU</b>	• difficult	• high	• low	• medium	• medium	•••••
<b>PyCloP</b>	• difficult	• high	• low	• medium	• very high	•••••
<b>BOP</b>	• difficult	• high	• low	• very high	• high	•••••
<b>DCC/HOBT</b>	• very difficult	• medium	• medium	• high	• low	•••••
<b>DCC</b>	• very difficult	• low	• high	• high	• low	•••••

## ®T3P – Qualities Desired in the Ideal Coupling Agent

The **Ideal Amide Coupling Agents** give high yields with low epimerization. They pose no health or environmental threats, and the resulting by-products allow for simple phase extraction instead of cost intensive chromatography. ®T3P has all of these qualities.

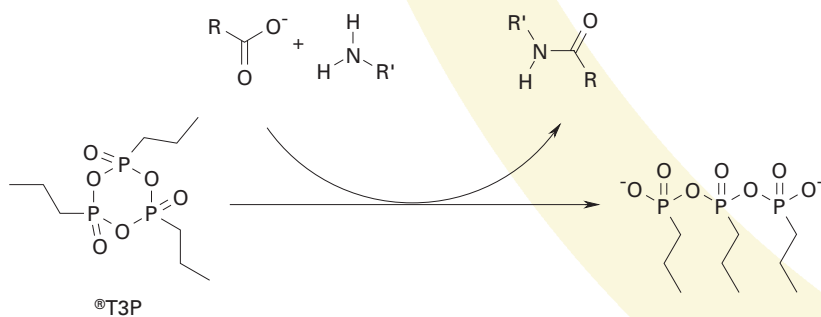
®T3P converts the oxygen of a carboxylic acid into an ionic leaving group, which is easily extracted from the product – even on a commercial scale. This makes ®T3P the first choice in the synthesis of high value products – particularly in late stage syntheses.



DCC Coupling: cost intensive purification, low yields, high epimerization



TBTU/HBTU Coupling: cost intensive purification, high epimerization



®T3P Coupling: easily purification, low epimerization

### ®T3P – The Qualities You Need

- Easy purification
- High yields
- Low epimerization
- Reduced overall process costs
- Commercial scale advantages
- Nontoxic, nonallergenic
- Readily available ex stock
- Detailed technical packages for application available

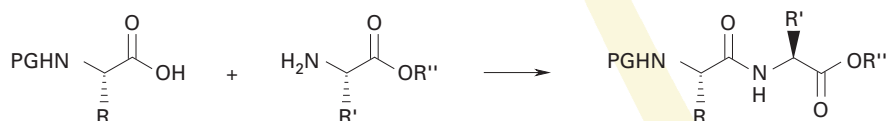


Concerted Efforts Moving You Downstream

## ®T3P – Tailor-made for Your Application

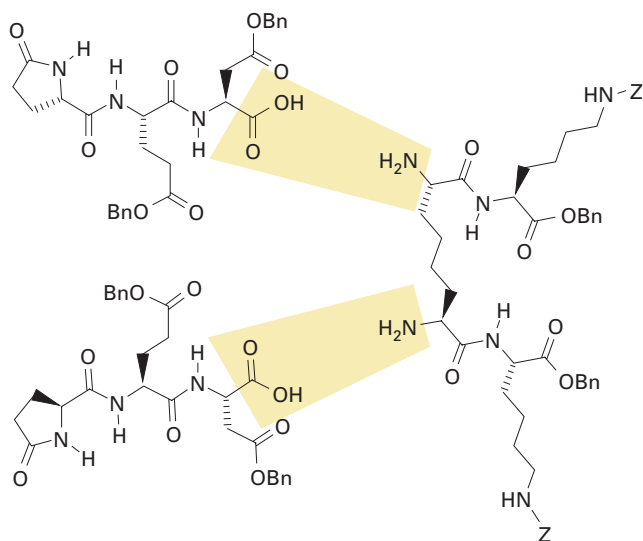
**Standard Lab Procedure** for Amide/Peptide Bond Formation with ®T3P. A mixture of 1.0 mmol acid, 1.0 mmol amine and 2.5 mmol base in an appropriate solvent (10 mL) is cooled to 0...20°C.

1.15...1.20 mmol ®T3P solution (50% w/w) are added dropwise, while maintaining the reaction temperature over 30...60 minutes. The mixture is allowed to warm to room temperature.



**Product Isolation.** The reaction is quenched with water or 1 N NaOH, the phases are separated, and the organic layer is stripped to remove residual water. The product is isolated as appropriate.

Detailed protocols and technical packages for specific compound classes are available on request.



**®T3P – The Coupling Performance Leader.** Recent performance comparisons between ®T3P and other leading coupling agents continue to show ®T3P as the leader in end product purification, epimerization, yield, toxicity, and overall process costs.

*J. Hiebl et al., J. Pept. Res. 1999, 54, 54*



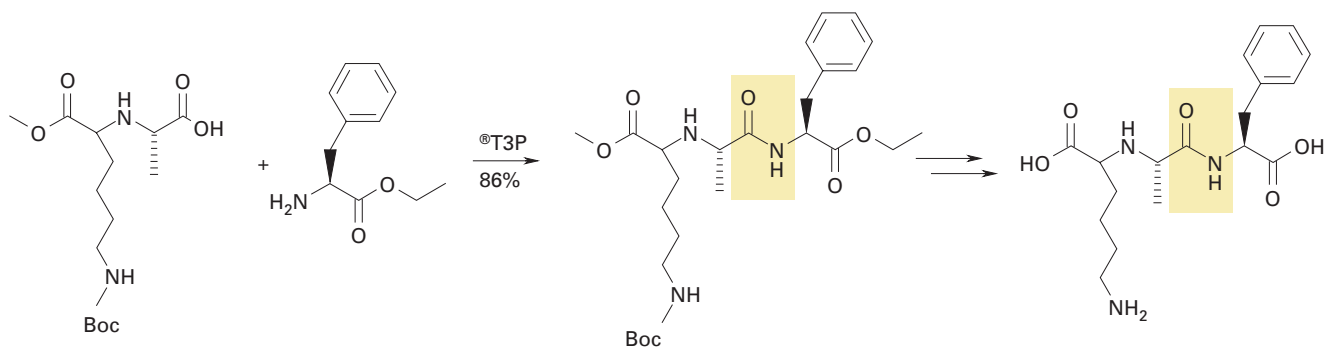
In Synch With Low Epimerization

## ®T3P – The Value in High-value Products

### ®T3P as a Classical Peptide Coupling Reagent.

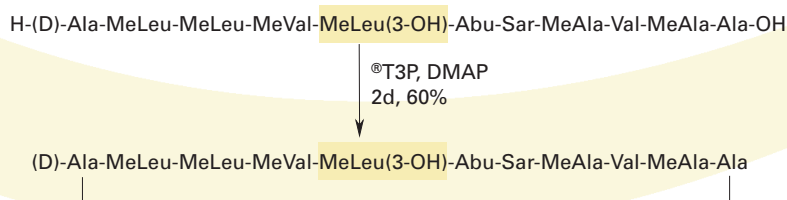
®T3P allows for the high yield and low epimerization synthesis of peptide libraries. A library for screening tests can easily be obtained without the need for costly column purification due to the ionic nature of the by-products.

*R. Escher, P. Büning, Angew. Chem. Int. Ed.*  
1986, 108, 277 [264]



**®T3P – The Choice in Cyclizations.** The selectivity of ®T3P allows the final step of synthesizing high-value molecules like cyclosporin derivatives to proceed without additional steps to protect the MeLeu(3-OH) alcohol.

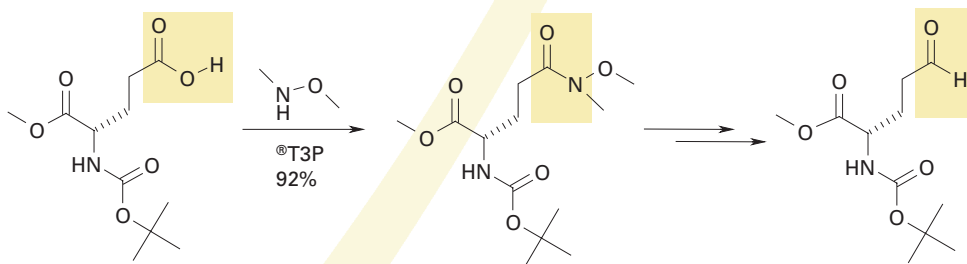
*Wisconsin Alumni Research Foundation WO*  
98 / 46247



**High ee Chiral Weinreb Amides.** Under mild conditions,  $\text{®T3P}$  is the ideal activator for the formation of Weinreb amides. The selectivity of  $\text{®T3P}$  results in low levels of epimerization. Weinreb

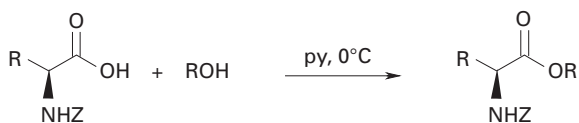
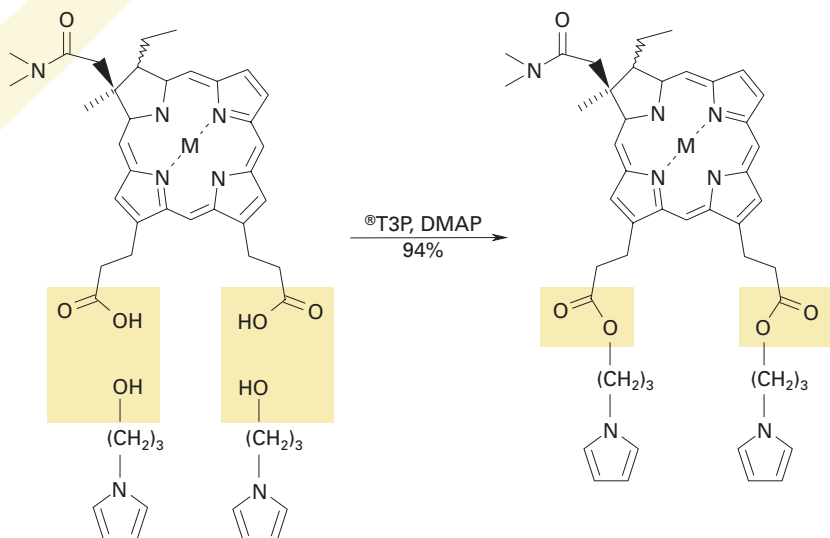
amides can be further functionalized, e.g. they can be reduced to the respective aldehydes.

*H. Kessler et al., Angew. Chem. Int. Ed. 1997, 36, 1191 [1240]*



**Esters with  $\text{®T3P}$ .** Due to the high selectivity and low epimerization characteristics of  $\text{®T3P}$ , this coupling agent is also ideal for the formation of complex and sensitive esters.

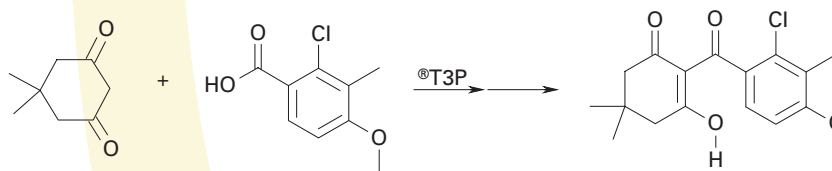
*F.-P. Montforts et al., Eur. J. Org. Chem. 2001, 1681-1687*



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-Tyr(tBu)-O-tBu, 76%

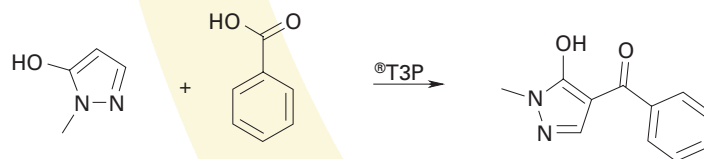
## ®T3P – The Power in Condensations

**C,C-coupling Reactions.** ®T3P converts the oxygen of carboxylic acids into a leaving group.



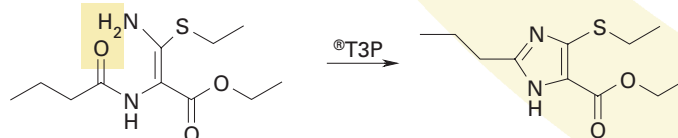
®T3P as a coupling agent for pyrazoles. Pyrazoles are frequently found in today's active pharmaceutical ingredients.

*Bayer, DE 100 63 493*



**Formation of Substituted Heterocycles.** ®T3P – “liquid organic P<sub>2</sub>O<sub>5</sub>” as a classical condensation agent.

*Hoechst, WO 99 / 37620*



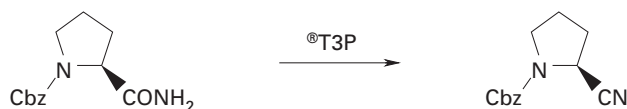


Focused on Easy Workup

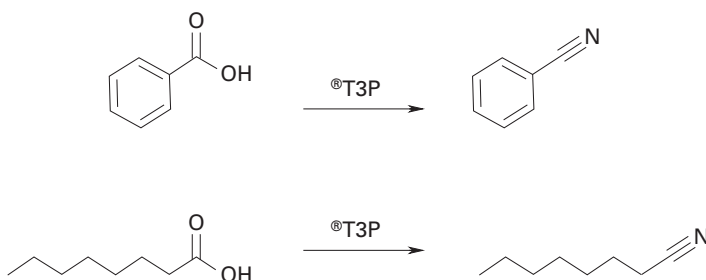
## ®T3P – New Applications in Dehydrations and Condensations

We have developed a variety of new applications of ®T3P in dehydration and condensation reactions – all of which are characterized by the general advantages of ®T3P applications (easy application, economic processes, high selectivities and yields, excellent product purities, no epimerization). Some examples are shown below. Detailed technical packages including more new applications are available on request.

**Nitriles from Amides and Acids.** Under very mild conditions, ®T3P dehydrates aliphatic and aromatic amides to the respective nitriles in high yield and without racemization/epimerization.

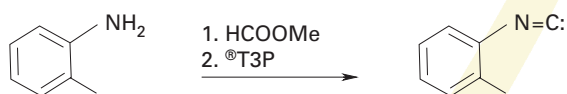


The direct conversion of acids to nitriles is possible with ®T3P and a nitrogen source, e.g. ammonia gas, ammonium chloride or certain primary amines. This reaction works both with aliphatic and aromatic acids and the yields are typically in the 90–97% range.

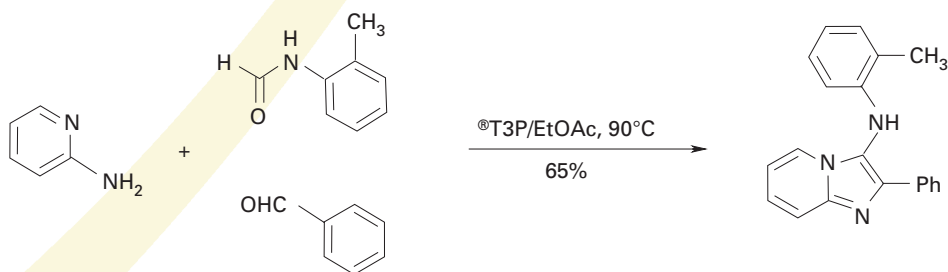


**Isonitriles from Formamides.** ®T3P dehydrates formamides to the respective isonitriles and can be used in several isonitrile applications. The system

®T3P/formamide can be considered a storage form for isonitriles. Again, the high selectivity and easy application result in a very economical approach.

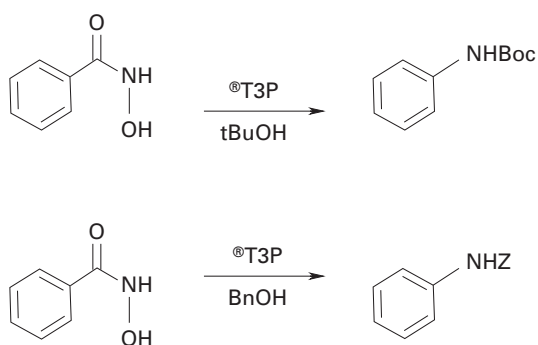


One application example is shown below, demonstrating the high potential of ®T3P in isonitrile chemistry and in the formation of heterocycles.



**From esters to protected anilines.** ®T3P can be used for amine generating rearrangements of hydroxamic acids, which in turn are available from esters and hydroxylamine. Overall, this results in the conversion of esters to protected

anilines, with a broad flexibility of protecting groups at nitrogen. Using benzyl alcohol yields Z-protected anilines; the application of tert.-butanol yields Boc-protected anilines.





Your All-inclusive Solution



## ®T3P – The Value-added Alternative

**Archimica's Free Application Program.** Our 20 years of industrial experience with ®T3P provide the basis for our synthesis experts to integrate the coupling and extraction steps required into your upstream and downstream process stages. This is a part of our Free Application Program for your commercial scale-up.

Archimica provides this free program under a Confidential Disclosure Agreement. This way, the knowledge we develop in coordination with you, stays in your control. The purpose of this

program is to allow you to build expertise with ®T3P while our experienced staff quickly evaluate and examine your defined process targets in yield, selectivity, and quality. This enables us to determine how ®T3P can best fit your process needs.

If needed, our experience with different processes allows us to tackle the question of proper disposal of the low toxic and water soluble decomposition products of ®T3P while handling any treatment issues that your process may encounter.

## ®T3P – Your Tailor-made Solution

**Specification.** ®T3P is currently supplied as a 50% (w/w) solution in N,N-dimethylformamide, ethyl acetate, butyl acetate or in any other solvent appropriate to the needs of our customers. We are available to answer your questions, and will gladly discuss your individual needs with you.

**Quality Management.** ®T3P is produced in an DIN EN ISO 9001:2000 certified facility.

**Availability.** ®T3P is manufactured on a regular basis and is generally available from stock.

**Notification.** ®T3P is a registered trademark in accordance with statutory regulations. Before ®T3P can be released to our customers (even in sample quantities) we require the completion of our end use documentation.

Molecular weight	318.2 g/mol
Empirical formula	(C <sub>3</sub> H <sub>7</sub> O <sub>2</sub> P) <sub>3</sub>
Assay ( <sup>31</sup> 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

®T3P

# Contacts

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