**SYNLETT Spotlight**

**Spotlight 472**

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Vijaykumar H. Thorat was born in 1982 in Osmanabad, India. He graduated with a B.Sc. in chemistry (2003) from the Dr. Babasaheb Ambedkar Marathwada University, Aurangabad and received his M.Sc. (2005) from the University of Pune. From 2008 to 2012 he worked as a Senior Research Fellow at the National Chemical Laboratory, Pune, India. Currently, he is pursuing his Ph.D. under the supervision of Assistant Professor Dasheng Leow at the National Tsing Hua University, Hsinchu, Taiwan.

Department of Chemistry, National Tsing Hua University, No. 101, Sec. 2, Kuang-Fu Road, Hsinchu 30013, Taiwan

E-mail: vijaykumarthorat@yahoo.com

**Introduction**

The de novo synthesis of peptides is one of the key interests of organic chemists. Dehydroamino acids are an important class of molecules and are widely recognized as excellent synthetic precursors for non-natural amino acids. They are also seen as structural units in many biologically active peptides. The 2-phthalimidoacrylates are dehydroamino acids derivatives. The amino and the carboxylic acid groups are protected as N-phthalimido and carboxylic ester groups. Although 2-phthalimidoacrylates are enamides, the olefin is substituted with electron-withdrawing groups. These features allow versatile modifications of the alkene under a myriad of reaction conditions.

The synthesis of 2-phthalimidoacrylates was first described by Brown and Smale in a three-step sequence starting from threonine methyl ester. Trost and co-worker shortened the synthesis to a single step using triphenylphosphine as a nucleophilic catalyst (Scheme 1). Phthalimide adds to various propiolates selectively at the α-position in excellent yields. This reaction provides convenient access to the 2-phthalimidoacrylates and is amendable to scaling up.

![Scheme 1 Synthesis of 2-phthalimidoacrylates](image)

2-Phthalimidoacrylates are very stable and can be kept on the benchtop for many years without any noticeable decomposition. They have an indefinite shelf life if they are kept at 4 °C. In addition, methyl 2-phthalimidoacrylate is commercially available.

**Abstracts**

(A) **Rh-Catalyzed 1,4-Addition of Potassium Aryltrifluoroborates and Aryltrialkoxy silanes**

The rhodium-catalyzed 1,4-addition of potassium aryltrifluoroborates to 2-phthalimidoacrylates was reported by the Genet group. Frost and co-workers extended the aryl coupling partner to aryltrialkoxy silanes. These reactions furnish expedient access to unnatural α-amino acids.

![Reaction Equation](image)

(B) **Enantioselective Protonation Catalyzed by Chiral Guanidine**

Tan and co-workers achieved the enantioselective protonation of tert-butyl 2-phthalimidoacrylate with thiols using a chiral bicyclic guanidine derivative as a Brønsted base catalyst. Chiral cysteines were formed in excellent yields and enantioselectivities. The tert-butyl ester group was essential for obtaining high enantioselectivities.
(C) Asymmetric Protonation with 3-Substituted Oxindoles
The Xiao group reported the asymmetric protonation of ethyl 2-phthalimidoacrylate with 3-substituted oxindoles. They found that this reaction can be catalyzed by cinchona alkaloid derived thiourea catalysts to provide the products in excellent yields and enantioselectivities.\(^6\) The authors proposed a dual activation model for the transition state. The Michael donor was enolized by a tertiary amine, while the 2-phthalimidoacrylate interacted with the thiourea through dual hydrogen bonding.

(D) Michael Reaction of 2-Methylmalononitrile Catalyzed by a Diamine
Tong and Chiba developed an ethylenediamine-catalyzed intermolecular conjugate addition of 2-methylmalononitrile to methyl 2-phthalimidoacrylate. The addition proceeds in good yield.\(^7\)

(E) [3+2] Cycloaddition of Allenes Catalyzed by a Chiral Phosphepine
Fujiwara and Fu synthesized new chiral phosphepines with a 1,1′-biphenyl framework and used them to perform the catalytic enantioselective [3+2] cycloaddition of γ-substituted allenes with tert-buty1 2-phthalimidoacrylate in excellent yields and enantioselectivities.\(^8\)

(F) Pd(II)-Catalyzed Remote meta-Selective C–H Olefination
Yu and co-workers devised the concept of an end-on template, with linear coordinating a nitrile group as the handle for palladium(II)-catalyzed remote meta-selective C–H functionalization. Using ethyl 2-phthalimidoacrylate, they applied the same method to synthesize meta-substituted dehydroamino acids via C–H olefination of toluene derivatives.\(^9\)

(G) Enantioselective 1,3-Dipolar Cycloaddition Catalyzed by Ag(I)
The Deng group reported that in the presence of FOXAP ligand, silver(I) catalyzes the 1,3-dipolar cycloaddition of azomethine ylides with 2-phthalimidoacrylates in excellent regio- and enantioselectivities.\(^10\) This process provides an efficient access to chiral pyrrolidine derivatives.

(H) Hydroperfluoroalkylation via Radical Addition
The Yajima group demonstrated the addition of perfluoroalkyl radicals to ethyl 2-phthalimidoacrylate.\(^11\) The perfluoroalkyl radicals were generated by irradiation with a mercury lamp, and the intermediate was quenched by the hydrogen donor tris(trimethylsilyl)silane (TTMSS). They also installed Oppolzer’s sultam at the ethyl ester position and achieved excellent diastereoselectivities of >92:8.

References