

SYNLETT Spotlight 472

2-Phthalimidoacrylates

Compiled by Vijaykumar H. Thorat



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

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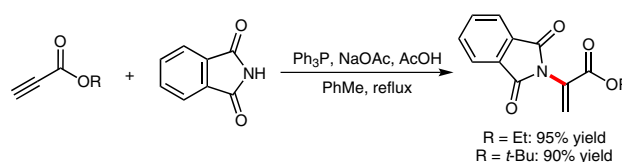
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Introduction

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.¹ Trost and co-worker shortened the synthesis to a single step using triphenylphosphine as a nucleophilic catalyst (Scheme 1).²

Phthalimide adds to various propiolates selectively at the α -position in excellent yields. This reaction provides convenient access to the 2-phthalimidoacrylates and is amenable to scaling up.



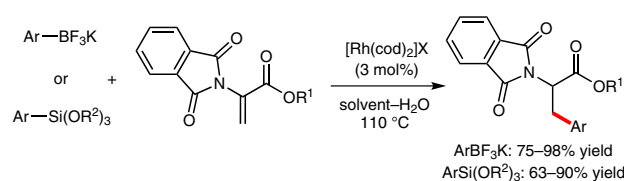
Scheme 1 Synthesis of 2-phthalimidoacrylates

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

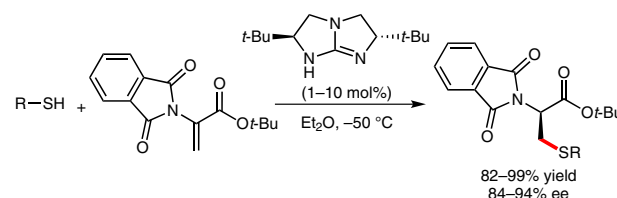
(A) Rh-Catalyzed 1,4-Addition of Potassium Aryltrifluoroborates and Aryltrialkoxysilanes

The rhodium-catalyzed 1,4-addition of potassium aryltrifluoroborates to 2-phthalimidoacrylates was reported by the Genet group.³ Frost and co-workers extended the aryl coupling partner to aryltrialkoxysilanes. These reactions furnish expedient access to unnatural α -amino acids.⁴



(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.⁵ Chiral cysteines were formed in excellent yields and enantioselectivities. The *tert*-butyl ester group was essential for obtaining high enantioselectivities.



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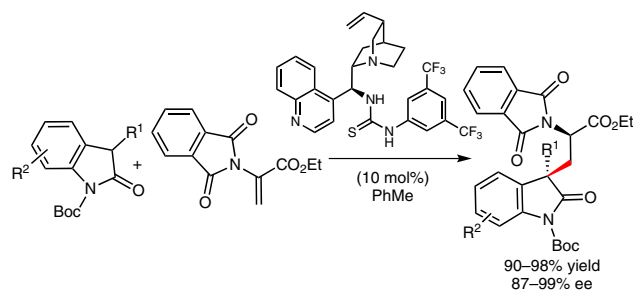
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DOI: 10.1055/s-0033-1339081; Art ID: st-2014-v0479-v

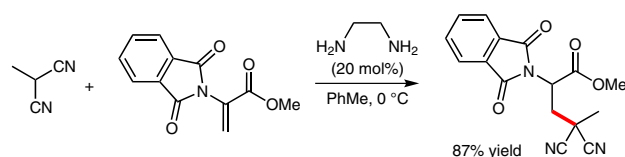
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(C) *Asymmetric Protonation with 3-Substituted Oxindoles*

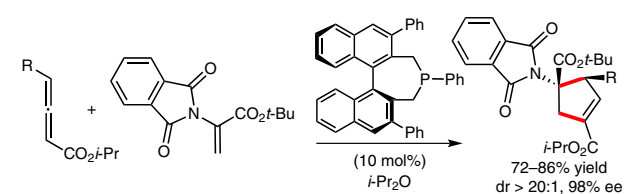
The Xiao group reported the asymmetric protonation of ethyl 2-phthalimidoacrylate with 3-substituted oxindoles. They found that this reaction can be catalyzed by cinchona alkaloid derived thiourea catalysts to provide the products in excellent yields and enantioselectivities.⁶ The authors proposed a 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*

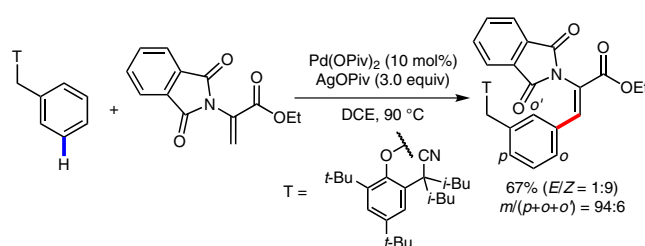
Tong and Chiba developed an ethylenediamine-catalyzed intermolecular conjugate addition of 2-methylmalononitrile to methyl 2-phthalimidoacrylate. The addition proceeds in good yield.⁷

(E) *[3+2] Cycloaddition of Allenes Catalyzed by a Chiral Phosphine*

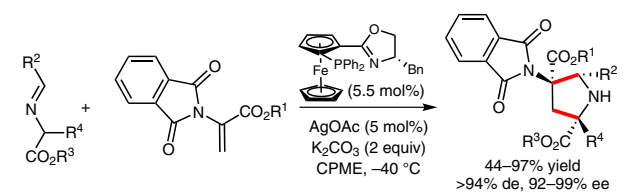
Fujiwara and Fu synthesized new chiral phosphines with a 1,1'-binaphthyl framework and used them to perform the catalytic enantioselective [3+2] cycloaddition of γ -substituted allenes with *tert*-butyl 2-phthalimidoacrylate in excellent yields and enantioselectivities.⁸

(F) *Pd(II)-Catalyzed Remote meta-Selective C–H Olefination*

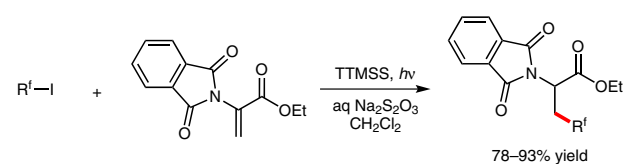
Yu and co-workers devised the concept of an end-on template, with linear coordinating a nitrile group as the handle for palladium(II)-catalyzed remote *meta*-selective C–H functionalization. Using ethyl 2-phthalimidoacrylate, they applied the same method to synthesize *meta*-substituted dehydroamino 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.



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