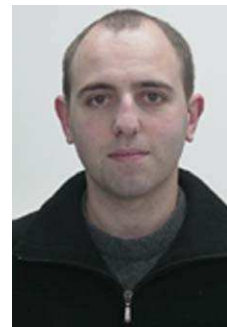


SYNLETT Spotlight 171

Benzophenone Imine

Compiled by Abel Crespo



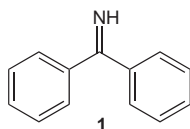
This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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Introduction

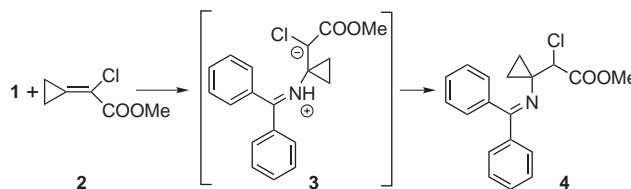
Benzophenone imine or (diphenylmethylene)amine (DPMA-H, **1**) is a valuable reagent in organic synthesis.¹ It is a commercially available liquid which is easily prepared by addition of phenylmagnesium bromide to benzonitrile followed by hydrolysis with methanol² or by reaction of benzophenone with ammonia.³



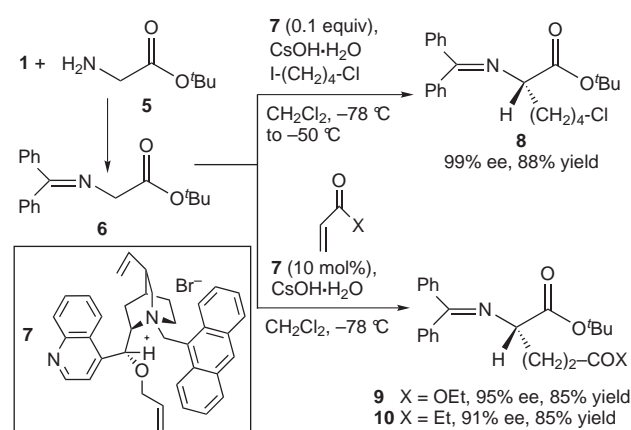
Synthetic applications of **1** have been historically related to peptide chemistry, specifically as protecting group of primary amines during the preparation of optically active α -amino acids.⁴ Used in conjunction with other anion-stabilising groups, **1** provides activation for proton abstraction. More recently, the development of highly efficient tin-free palladium-catalysed amination methodologies by the groups of Buchwald⁵ and Hartwig⁶ increased its synthetic utility as convenient ammonia surrogate in catalysed coupling reactions.

Abstracts

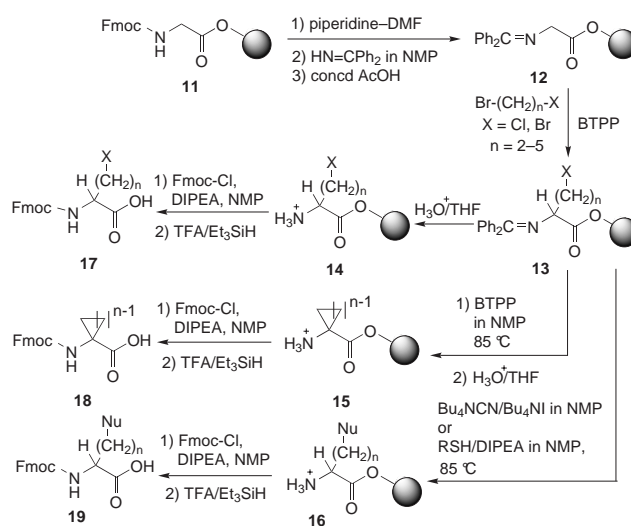
(A) A. de Meijere et al.⁷ have published the base-catalysed reaction of benzophenone imine (**1**) with methyl-2-chloro-2-cyclopropylideneacetate (**2**) to give 1,4-adduct **4**, which is a valuable intermediate in the synthesis of cyclopropyl- β -amino acids. The formal [2+4] cycloaddition of **1** and **2** affords substituted quinolines.



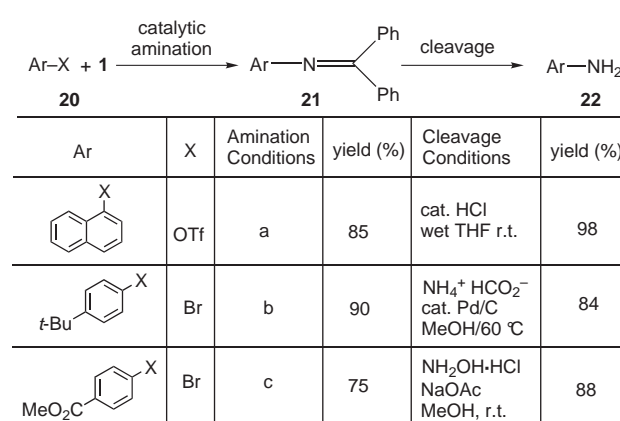
(B) DPMA-H (**1**) serves as amino-protecting group in the enantioselective synthesis of functionalized α -amino acids^{6,8} and small peptides⁹ using a chiral quaternary ammonium salt as catalyst.



(C) Benzophenone imine of glycine Wang resin (**12**) [prepared from Fmoc of glycine Wang resin (**11**) by treatment with piperidine–DMF and then DPMA-H in NMP and glacial acetic acid] can be alkylated with α,ω -dihaloalkanes affording the valuable reactive intermediate **13**. Synthetic manipulation at the living group (X), cleavage of protecting fragments and resin yield the side-chain-reactive unnatural amino acids **17–19**.¹⁰

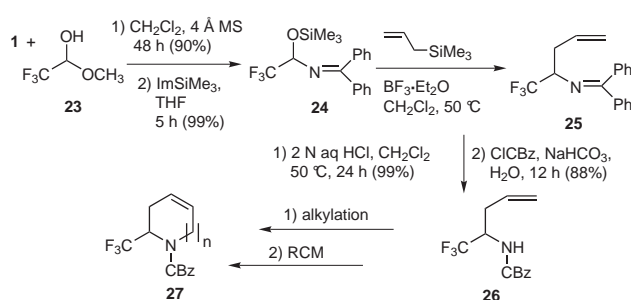


(D) DPMA-H (**1**) is employed in the Buchwald–Hartwig reaction as a convenient ammonia surrogate in the palladium- and nickel-catalysed amination of organic electrophiles **20**. The benzophenone imine adducts **21** can be isolated in pure form or cleaved directly to the corresponding primary anilines **22** under mild conditions by catalytic hydrogenation, treatment with hydroxylamine hydrochloride or a catalytic amount of HCl in wet THF.¹¹ A new series of improved catalysts for this transformation was recently documented.¹²



(a) 1 mol% Pd(OAc)₂, 1.5 mol% BINAP, 1.4 equiv Cs₂CO₃, THF, 65 °C, 16 h. (b) 0.25 mol% Pd₂(dba)₃, 0.75 mol% BINAP, 1.4 equiv NaOt-Bu, toluene, 80 °C, 13 h. (c) 2 mol% Pd(OAc)₂, 3 mol% BINAP, 1.4 equiv Cs₂CO₃, toluene, 100 °C, 6 h.

(E) Benzophenone imine (**1**) has been used in the preparation of the trifluoromethylated homoallylamine **26**, a useful starting material to achieve the synthesis of α -trifluoromethylated nitrogen heterocyclic compound **27** through an alkylation–ring-closure-metathesis (RCM)¹³ sequence.



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