SYNLETT
Spotlight 171

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

Benzophenone Imine

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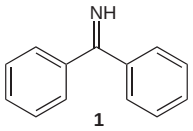
Introduction

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 methanol[2] or by reaction of benzophenone with ammonia.[3]

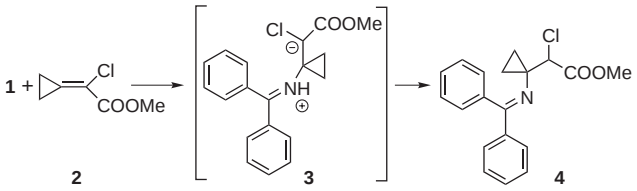


1

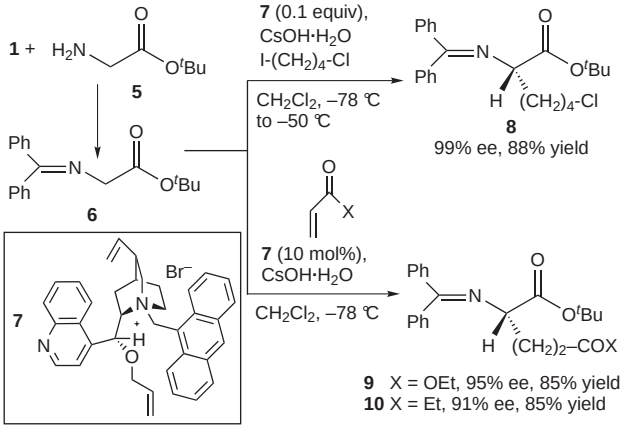
Synthetic applications of **1** have been historically related to peptide chemistry, specifically as protecting group of primary amines during the preparation of optically active α-amino acids.[4] Used in conjunction with other anion-stabilising groups, **1** provides activation for proton abstraction. More recently, the development of highly efficient tin-free palladium-catalysed amination methodologies by the groups of Buchwald[5] and Hartwig[6] 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 peptides[9] using a chiral quaternary ammonium salt as catalyst.



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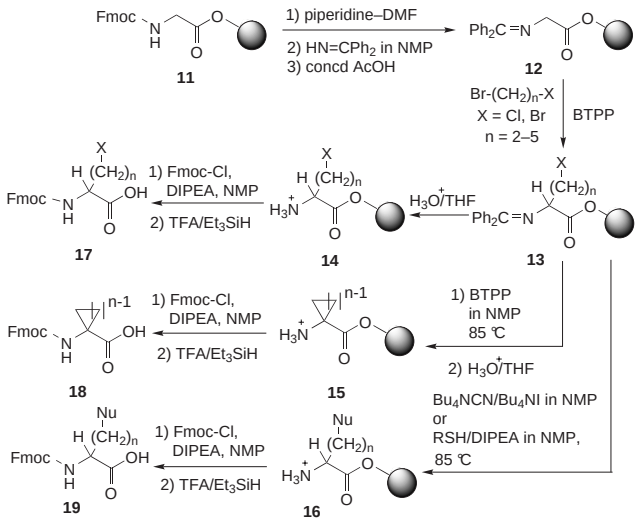
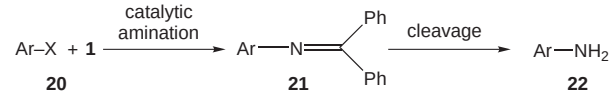
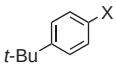
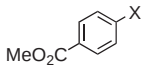
(C) Benzophenone imine of glycine Wang resin (**12**) [prepared from F-moc of glycine Wang resin (**11**) by treatment with piperidine–DMF and then DPMA-H in NMP and glacial acetic acid] can be alkylated with α,ω-dihaloalkanes affording the valuable reactive intermediate **13**. Synthetic manipulation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



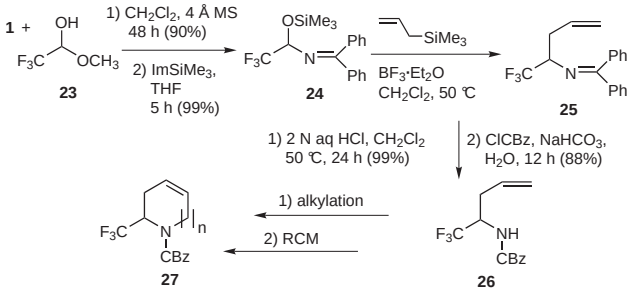
(D) DPMA-H (**1**) is employed in the Buchwald–Hartwig reaction as a convenient ammonia surrogate in the palladium- and nickel-catalysed amination of organic electrophiles **20**. The benzophenone imine adducts **21** can be isolated in pure form or cleaved directly to the corresponding primary anilines **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]



Ar	X	Amination Conditions	yield (%)	Cleavage Conditions	yield (%)
	OTf	a	85	cat. HCl wet THF r.t.	98
	Br	b	90	NH_4^+ HCO_2^- cat. Pd/C MeOH/60 °C	84
	Br	c	75	$NH_2OH{\cdot}HCl$ NaOAc MeOH, r.t.	88

(a) 1 mol% $Pd(OAc)_2$, 1.5 mol% BINAP, 1.4 equiv Cs_2CO_3, THF, 65 °C, 16 h. (b) 0.25 mol% $Pd_2(dba)_3$, 0.75 mol% BINAP, 1.4 equiv NaO*t*-Bu, toluene, 80 °C, 13 h. (c) 2 mol% $Pd(OAc)_2$, 3 mol% BINAP, 1.4 equiv Cs_2CO_3, 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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