SPOTLIGHT 2345

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.

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.

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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 anionstabilising 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. 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 enantio-selective synthesis of functionalized α -amino acids^{6,8} and small peptides⁹ 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.

(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

	alytic nation	→ Ar—N=	Ph -	cleavage	Ar—NH ₂
20		21	`Ph		22
Ar	Х	Amination Conditions	yield (%)	Cleavage Conditions	yield (%)
X	OTf	a	85	cat. HCI wet THF r.t.	98
t-Bu X	Br	b	90	NH ₄ ⁺ HCO ₂ ⁻ cat. Pd/C MeOH/60 ℃	84
 MeO ₂ C X	Br	С	75	NH ₂ OH•HCI NaOAc MeOH, r.t.	88

(a) 1 mol% Pd(OAc) $_2$, 1.5 mol% BINAP, 1.4 equiv Cs $_2$ CO $_3$, THF, 65 °C, 16 h. (b) 0.25 mol% Pd $_2$ (dba) $_3$, 0.75 mol% BINAP, 1.4 equiv NaO $_7$ -Bu, toluene, 80 °C, 13 h. (c) 2 mol% Pd(OAc) $_2$, 3 mol% BINAP, 1.4 equiv Cs $_2$ CO $_3$, 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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