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Highly Efficient Darzens Reactions Mediated by Phosphazene Bases under Mild Conditions

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The highly basic and poorly nucleophilic phosphazene base P_1-*t*-Bu promotes the Darzens condensation of α-halo esters with aromatic aldehydes affording α,β-epoxy esters in nearly quantitative yields under mild conditions and in short reaction times. The more basic P_4-*t*-Bu phosphazene was found useful with low reactivity aldehydes. These reactions can be performed in aprotic organic solvents of low polarity, thus minimizing the hydrolysis of α,β-epoxy esters which often accompanies the base-promoted Darzens condensations.

Introduction

Polyaminophosphazenes are extremely strong, chemically and thermally stable, non-ionic Brønsted superbases with pK_{BH+} values spanning the range from 27.6 to about 47 as determined or estimated in acetonitrile.[1–6] Besides their high basicity, the usefulness of phosphazene bases in producing highly reactive anions is due to the large size and charge delocalization of the phosphazenium ions, leading to weak cation−anion interactions.[7] In addition, the low nucleophilicity of phosphazene bases[1,3,4] and the high stability of phosphazenium cations enable smooth deprotonation processes from even very weakly acidic C–H bonds with limited side reactions.[8,9] Furthermore, the high solubility of polyaminophosphazenes in organic solvents such as hexane, toluene, DCM or THF allows conceiving novel approaches to base-promoted processes in organic media of low polarity.[10] Because of these properties, polyaminophosphazene bases are experiencing a recent surge of interest and applications in many novel synthetic methodologies. Indeed, phosphazene bases have been used as stoichiometric reagents or catalysts in a variety of reactions requiring the formation of reactive, or otherwise inaccessible, carbon nucleophiles.[11] Among these reactions, the addition of the highly reactive trifluoromethyl anion to carbonyl electrophiles,[12] aldol reactions, Michael additions,[12,13] activation of silylated pro-nucleophiles,[14] the addition of nucleophiles to alkenes and alkynes,[15] the reaction of aryl halides with alkali metal aryloxides or arylthiolates,[16] the amination of β-(hetero)arylethyl ethers[17a] or methoxy(hetero)arenes[17b] are worth mentioning. Furthermore, palladium-catalyzed C–N, C–O, and C–C cross-coupling reactions are also aided by phosphazene bases.[18] Moreover, these compounds are widely used in ring-opening polymerization reactions.[19]

Among base-promoted processes, the Darzens reaction, the condensation of α-halo esters with aldehydes or ketones to form glycidic esters, represents an interesting example that would benefit of the facile generation of carbon nucleophiles allowed by phosphazene bases. However, to the best of our knowledge, there are, to date, no examples of phosphazene bases used in this type of Darzens condensation. The Darzens reactions, having enjoyed a sustained development in recent years, enable the preparation of α,β-epoxy carbonyl compounds which are recognized as important synthetic intermediates to construct complex organic frameworks.[20–23] The scope and synthetic significance of this reaction have enlarged as the result of the diversity of α-halo carbonyl compounds that can be used. Indeed, in addition to α-halo esters, α-halo amides,[24] α-halo nitriles[24,25] and α-haloketones[26] have been used as pro-nucleophiles. Furthermore, aza-Darzens reactions were developed using imines, sulfinimines or *N*-sulfonyl imines as electrophile components.[27] Other compounds with active methylene groups and bearing suitable leaving groups such as α-halosulfones[28] or ammonium[29] and sulfonium ylides[11l,13f, 30] have also been successfully employed as pro-nucleophiles. Lewis and Brønsted acid-catalyzed Darzens reactions have also been reported for α-diazoamides and diazoesters.[31] Nowadays, in their base-promoted version, the Darzens reactions of α-halo esters with aromatic aldehydes are most commonly performed in the presence of anionic bases such as alkali metal hydroxides, carbonates or alkoxides,[32] sodium amide, LDA, LiHMDS or *n*-butyllithium,[33] very often with pre-formation of the reactive ester enolate anion. In the case of α-chloroketones and α-chloroamides, the use of phase transfer agents in association with aqueous metal hydroxides has now become a paradigm leading to α,β-epoxy carbonyl compounds in moderate-to-

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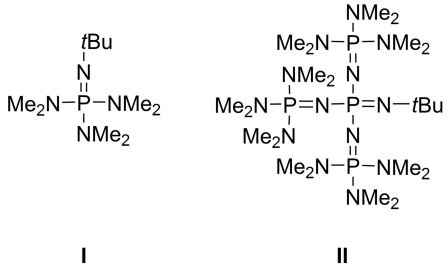
excellent yields and stereoselectivity.[34] However, with respect to α,β-epoxy esters, their preparation by means of Darzens reactions remains far from ideal. Indeed, as far as α-halo esters are concerned, hydrolysis of the *trans* epoxy esters has been reported,[35] even in the case of *tert*-butyl esters.[36] This reactivity has been invoked as a possible explanation for the low yields or the exclusive *cis*-selectivity observed in some cases.[24b] In addition, in the reactions promoted by metal alkoxides, the formation of unwanted side products such as α-chlorocinnamate esters[37] was reported and the formation of α-chloro-β-lactones was even dominant in the case of the Darzens condensations involving phenyl esters of α-chlorocarboxylic acids promoted by lithium *N*-cyclohexyl-*N*-isopropylamide.[38] We considered that the strength of phosphazene bases and their inertness as nucleophiles could offer some advantages in the development of a Darzens condensation in aprotic organic solvents of low polarity.[39] Here, we describe the results so far obtained from exploring two phosphazene bases. Exploring a series of solvents and reaction conditions; the best conditions were then used to investigate the scope of the reaction, the role of the pro-nucleophile and the stereoselectivity of the process.

Results and Discussion

To test the utility of phosphazene bases in Darzens reactions, we used the two readily available bases P_1-*t*-Bu **I** (pK_{BH+} = 26.89)[1b] and P_4-*t*-Bu **II** (pK_{BH+} = 42.7),[1d] as shown in Figure 1, for the condensation of methyl chloroacetate (**1a**) with 4-bromobenzaldehyde (**2a**) taken as model system (Table 1).

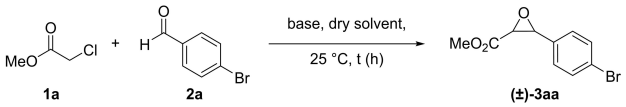
A preliminary solvent screening was performed considering acetonitrile, DCM, THF and toluene (Table 1); this identified acetonitrile (dielectric constant, ε = 37.5) as the optimal choice. Reaction in this solvent resulted in complete conversion of the starting materials within 6 h, affording **3aa** in 92% isolated yield (Table 1, entry 1). In the numbering systems of the condensation products, the first letter refers to the α-halo ester, while the second identifies the aldehyde. Lowering the reaction temperature to −25 °C had little impact on the outcome, and **3aa** was obtained in 86% isolated yield after 10 h (Table 1, entry 2). Quite remarkably, the use of a significantly less polar solvent such as dichloromethane (ε = 8.93) provided similar results to that of acetonitrile in terms of yield although requiring a longer reaction time (Table 1, entry 3). The reactivity



I **II**

Figure 1. Phosphazene bases used in this study.

Table 1. Survey of bases and solvents for the Darzens reaction of methyl chloroacetate (**1a**) with 4-bromobenzaldehyde (**2a**).[a]



1a **2a** **(±)-3aa**

Entry	Base	Solvent	ε	Time [h][b]	Yield [%][c,d]	*d.r.*[d,e]
1	**I**	MeCN	37.5	6	92	1/0.9
2[f]	**I**	MeCN	37.5	10	86	0.9/1
3	**I**	DCM	8.93	16	90	1/0.85
4	**I**	THF	7.58	24	83	1/0.94
5	**II**	THF	7.58	24	57	1/0.85
6	**I**	Toluene	2.38	48	66	0.88/1

[a] Unless otherwise stated, all Darzens reactions were carried out using 0.5 mmol of the aldehydes and a stoichiometry of 1.5:1:1.5 **1a**/**2a**/(**I** or **II**) in 2 mL of solvent at 25 °C. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of two experiments. [e] Determined by ^{1}H NMR analysis of the crude reaction mixture. [f] Reaction carried out at −25 °C.

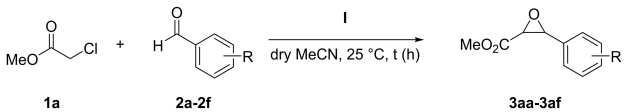
in DCM is also remarkable because this is a solvent usually not suitable for base-promoted Darzens reactions of α-halo esters. THF, with a dielectric constant of 7.58, provided the desired epoxide **3aa** in 83% yield in 24 h (Table 1, entry 4).

Given the long reaction time required using this solvent, the Darzens condensation was also performed with the stronger phosphazene base, P_4-*t*-Bu **II**, obtaining **3aa** in 57% yield after 24 h (Table 1, entry 5). However, the use of P_4-*t*-Bu **II** instead of P_1-*t*-Bu **I** resulted in a relatively complex mixture with formation of unidentified byproducts likely because of the exceedingly high strength of this base. Using a solvent of even lower polarity such as toluene (ε = 2.38) gave impractically long reaction times and poor overall yield of the product (Table 1, entry 6).

In all cases, the *cis* and *trans* α,β-epoxy esters were obtained in a ratio close to 1:1, in line with the high reactivity of the enolate anion obtained under these conditions. Not unexpectedly, other weaker organic bases such as Hünig's base, a typical hindered tertiary amine, or Proton Sponge® with a pK_{BH+} of 18.62,[40] did not result in conversion of the reagents. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), despite a pK_{BH+} of 24.34 measured in acetonitrile,[40] very close to that of P_1-*t*-Bu **I**, acted as a nucleophile under these reaction conditions.[41] Overall, the best conditions required the use of 1.5 equiv. of base **I**, dry acetonitrile as solvent and a 0.25 M concentration of reagents at a reaction temperature of 25 °C.

The scope of the reaction was assessed by considering a series of model aromatic aldehydes carrying different substituents at the *para*, *meta* or *ortho* position and methyl chloroacetate (**1a**) as the pro-nucleophile component (Table 2). Yields comparable to those obtained in the case of **2a** were obtained with 4-chlorobenzaldehyde (**2b**) which gave the epoxy ester **3ab** in 92% yield after 6 h, while the reaction of benzaldehyde (**2c**) was more sluggish, affording product **3ac** in 83% yield only after 16 h. With 4-nitrobenzaldehyde (**2d**), the epoxide was obtained in 81% yield within one hour, while with aldehydes **2e** and **2f**, carrying the electron-donating 4-methyl and 4-methoxy groups, the α,β-epoxy esters were obtained in 87%

Table 2. Darzens reactions of methyl chloroacetate (**1 a**) with aromatic aldehydes **2 a**-**2 h** in the presence of the phosphazene base P_1-*t*-Bu **I**. All reactions were carried at on a 0.5 mmol scale using a 1.5 : 1 : 1.5 **1 a**/**2**/**I** molar ratio in 2 mL of solvent at 25 °C.

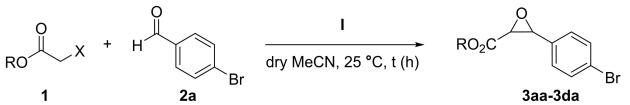


1a 2a-2f 3aa-3af

Aldehyde	R	Time [h]	Yield [%][a]	d.r.[b]
2 a	*p*-Br	6	92	1/0.9
2 b	*p*-Cl	6	92	1/0.9
2 c	H	16	83	1/0.75
2 d	*p*-NO_2	1	81	1/0.94
2 e	*p*-Me	16	87	1/0.85
2 f	*p*-OMe	48	74	0.9/1
2 f[c]	*p*-OMe	1	82	1/1
2 g	*o*-Br	6	84	1/1
2 h	*m*-OMe	16	91	1/0.8

[a] Yields of isolated products as the average of two experiments. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Reaction performed at −10 °C in THF on a 0.15 mmol scale using base **II**, single run.

Table 3. Darzens reaction of α-halo esters **1 a**–**1 d** and 4-bromobenzaldehyde (**2 a**) promoted by the phosphazene base P_1-*t*-Bu **I**.[a]



1 2a 3aa-3da

Entry	α-halo ester	R, X	Time [h][b]	Yield [%][c]	d.r.[d,e]
1	**1 a**	Me, Cl	6	92	1/0.9
2	**1 b**	Me, Br	16	85	1/0.9
3	**1 c**	*t*Bu, Cl	16	92	1/0.7
4	**1 d**	*t*Bu, Br	36	84	1/0.7

[a] All Darzens reactions were carried out on a 0.5 mmol scale using a 1.5 : 1 : 1.5 **1 a**–**1 d**/**2 a**/**I** molar ratio in 2 mL of acetonitrile at 25 °C. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of two experiments. [e] Determined by ^{1}H NMR analysis of the crude reaction mixture.

and 74% yield, respectively, albeit requiring a prolonged reaction time. The relatively low isolated yield of **3 af** arises from its reduced stability during chromatographic purification; indeed, using flash chromatography, variable amounts of the vicinal diols, formed by the opening of the epoxide ring, could be isolated. The 2-bromobenzaldehyde (**2 g**) provided the desired epoxide **3 ag** in 84% yield with a *d.r.* of 1/1, suggesting that the steric hindrance at the *ortho* position did not affect the diastereoselectivity of the reaction. As expected on the basis of electronic effects, aldehyde **2 h**, with the methoxy group at the *meta* position, gave the desired product **3 ah** in a better yield (91%) and after a shorter reaction time with respect to aldehyde **2 f**. In none of the cases discussed above that involve the use of P_1-*t*-Bu **I**, the formation of unwanted byproducts could be observed from analysis of the crude reaction mixture. For 4-nitrobenzaldehyde (**2 d**) and 4-methoxybenzaldehyde (**2 f**) that are, respectively, the most and the least reactive aldehydes in the panel, the condensation reactions were also carried out by using the phosphazene base P_4-*t*-Bu **II** in THF at −10 °C. In the former case, extensive decomposition occurred, while in the latter case, 82% yield of the product was achieved in 1 h (Table 2).

The sensitivity of the reaction yield and time on the nature of the halogen and/or alkoxy group carried by haloester **1** was assessed by using 4-bromobenzaldehyde (**2 a**) in the presence of P_1-*t*-Bu **I**, considering methylbromoacetate (**1 b**), *tert*-butylchloroacetate (**1 c**) and *tert*-butylbromoacetate (**1 d**) in addition to methylchloroacetate (**1 a**) as the pro-nucleophile components.

As in the previous cases, reactions were performed in dry acetonitrile at 25 °C (Table 3). Chloroesters provided faster reactions with respect to the corresponding bromoesters (Table 3, entry 1 vs. entry 2; entry 3 vs. entry 4), consistently with the expected higher acidity of the protons in the alpha position to the ester function of **1 a** with respect to those of **1 b** or those of **1 c** with respect to the alpha protons of **1 d**, and a rate-limiting deprotonation of the halo ester. The *tert*-butyl esters reacted at a slower rate with respect to the methyl esters (Table 3, entry 1 vs. entry 3; entry 2 vs. entry 4), and the introduction of the *tert*-butyl group only slightly affected the diastereoselectivity of the reaction. Overall, these data support a high reactivity of the "naked" enolate anions[42] formed by deprotonation of esters **1 a**–**1 d** which are only weakly associated with the phosphazenium cations.

The low *cis*/*trans* selectivity observed in these reactions could be either the result of the high reactivity of the ester enolate anions or due to a base-catalyzed epimerization of the reaction products because of the high strength of P_1-*t*-Bu **I** and the acidity of the C–H proton in position 2 of epoxide **3** (Figure 2).

In order to characterize the system, we tested the diastereoisomeric stability of *trans*-epoxide **3 ad** in the presence of P_1-*t*-Bu **I**, Figure 2. For this study *trans*-epoxide **3 ad** with a *cis*/*trans* diastereoisomeric ratio of 1/10, obtained by reaction of **1 a** and **2 d** with cesium carbonate in acetonitrile, was co-dissolved with base **I** in acetonitrile at the same concentration used in the

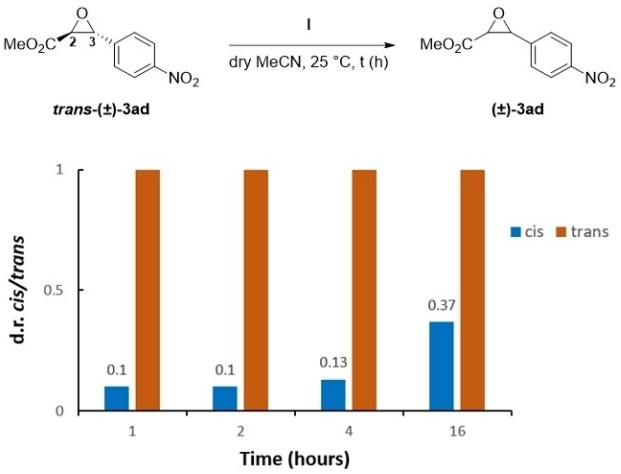


Figure 2. Time course of the degradation of *trans*-epoxide **3 ad** in the presence of P_1-*t*-Bu **I**.

Darzens reactions and, after given time intervals, the reaction mixture was analyzed by ^{1}H NMR spectroscopy.

This analysis showed that *trans*-epoxide **3 ad** does not undergo epimerization in four hours, which is four times larger than the time required for the synthesis of **3 ad** under the conditions reported in Table 2. The apparent increase in the *cis*/*trans* ratio observed at 16 h was thus due to the selective degradation to unidentified products of the *trans*-epoxide as evidenced by ^{1}H NMR analyses.

Conclusion

In summary, the Darzens reactions of α-halo acetate esters with aromatic aldehydes proceed smoothly in the presence of phosphazene bases, affording α,β-epoxy esters without side products. Acetonitrile, DCM or THF are suitable solvents for these reactions, and reaction times are inversely correlated to the dielectric constants of the solvents. The experimental results suggest that base P_1-*t*-Bu **I** should be preferred over base **II** when the reaction involves aromatic aldehydes carrying electron-withdrawing groups. In contrast, base **II** is more suited when the aldehydes carry electron-donating substituents. In all of the cases analyzed, and with a proper selection of the base, the reaction afforded α,β-epoxy esters with a *cis*/*trans* ratio of 1 to 1 in nearly quantitative yields and with short reaction times. Moreover, the reaction work-up is straightforward.

Experimental Section

General Information. Unless otherwise noted, all reactions were performed in oven-dried or flame-dried glassware. All reactions were performed in dry solvents under a nitrogen atmosphere. Air-sensitive reagents and solutions were transferred via a syringe and were introduced to the apparatus through rubber septa. All reagents were purchased from Sigma-Aldrich and used as received. All solvents were purchased from Sigma-Aldrich. Solvents for chromatography including cyclohexane and ethyl acetate were HPLC grade and used as received. Analytical thin layer chromatography (TLC) was performed on silica gel 60 RP-18F254S pre-coated plates with visualization under short-wavelength UV light and by dipping the plates with Pancaldi solution (ammonium molybdate and cerium(IV) sulfate in 4% sulfuric acid) followed by heating. Flash column chromatography was performed using Biotage® SNAP Cartridge KP-Sil 10 g, Biotage apparatus and the indicated solvent mixtures. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) on a Bruker UltraShieldTM 400 MHz spectrometer. Spectra were referenced to tetramethylsilane. Chemical shifts (δ) are reported in parts per million (ppm), and multiplicities are indicated as s (singlet), d (doublet), m (multiplet). Coupling constants, *J*, are quoted in Hz. ^{1}H and ^{13}C NMR assignments were corroborated by 1D and 2D experiments (gCOSY, gHSQC, ROESY sequences). ESI-mass spectra were recorded on AcquityTM Ultra Performance LC apparatus and are reported as (m/z): a) column: Acquity UPLC CSH C18 column (50 mm × 2.1 mm i.d. 1.7 μm particle size) at 40 °C; b) solvents: A = 0.1% *v*/*v* solution of HCOOH in water B = 0.1% *v*/*v* solution of HCOOH in acetonitrile; c) gradient: from 3% to 99.9% of solvent B; d) flow rate: 1 mL/min; e) acquisition stop time: 2.0 min.

General procedure for the preparation of compounds (±)-3 in the presence of base I. To a solution of aldehyde **2 a**-**2 h** (0.5 mmol, 1.0 equiv.) and α-halo ester **1 a**-**1 d** (0.75 mmol, 1.5 equiv.) in anhydrous acetonitrile (2 mL), P_1-*t*-Bu **I** (187 μL, 0.75 mmol) was added at 25 °C. The resulting mixture was stirred at 25 °C. The reaction mixture was concentrated under reduced pressure to yield the crude compound. The crude compound was purified by flash chromatography on silica gel using a mixture of cyclohexane/ethyl acetate 90/10 as eluent to yield compound **(±)**–**3**.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: α,β-epoxy esters · α-haloesters · carbon nucleophiles · polyaminophosphazenes · superbases

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