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P(NMe$_2$)$_3$-Mediated Umpolung Alkylation and Nonylidic Olefination of α-Keto Esters

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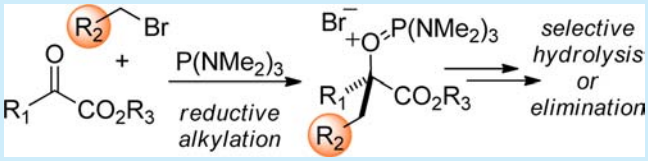
Supporting Information

ABSTRACT: A commercial phosphorus-based reagent (P(NMe$_2$)$_3$) mediates umpolung alkylation of methyl aroylformates with benzylic and allylic bromides, leading to either Barbier-type addition or ylide-free olefination products upon workup. The reaction sequence is initiated by a two-electron redox addition of the tricoordinate phosphorus reagent with an α-keto ester compound (Kukhtin−Ramirez addition). A mechanistic rationale is offered for the chemoselectivity upon which the success of this nonmetal mediated C−C bond forming strategy is based.



The one-pot reductive alkylation of carbonyl compounds with alkyl halides (Barbier reaction) is a versatile C−C bond forming reaction in organic synthesis.[1] Transformations of this type are most commonly promoted by reducing metals (i.e., Mg, Zn, In, etc.), being mechanistically initiated by single electron transfer (ET) from the reductant to either the organic halide or the carbonyl group, with subsequent ET delivering the observed products of reductive two-electron C−C bond formation.[2] Conceptually analogous transformations should also be available through polarity inversion of a carbonyl group[3] by formal two-electron reduction. In connection with this notion, trivalent phosphorus derivatives are known to undergo Kukhtin−Ramirez redox addition with α-dicarbonyl compounds (**1**) to give 1:1 adducts formulated (depending on substituents) as either dioxaphospholene (**2**) or oxyphosphonium enolate (**2′**) (Figure 1).[4] In effect, this transformation can

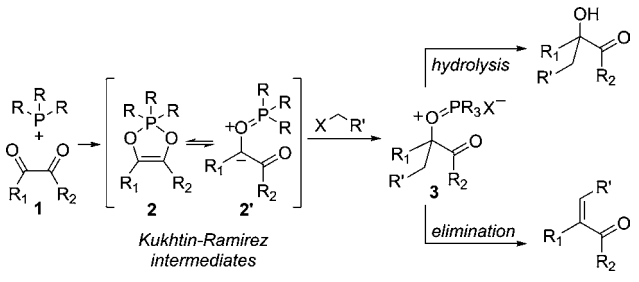


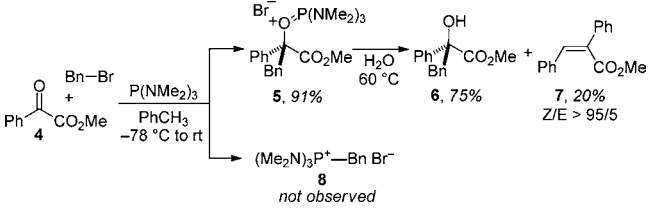
Figure 1. Umpolung C−C bond formation via Kukhtin−Ramirez intermediates.

be viewed as a two-electron reduction of the α-dicarbonyl compound resulting in polarity inversion of a carbonyl function. Congruent with this view, adducts **2**/**2′** have been shown to react as *C*-nucleophiles with a variety of reagents, including protic,[5] C_{sp^2}-based,[6] and heteroatom-based[7] electrophiles.

For the purpose of reductive C−C bonding transformations, we were interested in interception of **2**/**2′** with C_{sp^3}-based electrophiles (Figure 1).[8] This pursuit was motivated by the notion that the inherently closed-shell conditions of *P*-mediated reductive alkylation would offer useful chemoselectivities and functional group compatibilities as compared to dissolving metal methods. We report herein the chemoselective interception of the Kukhtin−Ramirez intermediates with alkylating reagents through reductive C−C bond formation to yield intermediate alkoxyphosphonium salts, which can be transformed under defined conditions into either corresponding tertiary alcohols through hydrolysis or trisubstituted *Z*-alkenes through elimination (Figure 1).

The reaction depicted in Scheme 1 illustrates a specific implementation of the aforementioned approach: a solution of

Scheme 1. Barbier-like Addition of Benzyl Bromide to Methyl Benzoylformate Mediated by P(NMe$_2$)$_3$



both methyl benzoylformate (**4**) and benzyl bromide in toluene at −78 °C was treated with tris(dimethylamino)phosphorus. Upon warming to ambient temperature with stirring for 2 h, a white solid precipitated and was collected by filtration in 91% yield. Although simple phosphonium formation (**8**) by direct quaternization of P(NMe$_2$)$_3$ with BnBr might be expected under these conditions, spectral and structural characterization unequivocally demonstrate the formation of alkoxyphosphonium salt **5** through a carbonyl umpolung alkylation.[9] Evidently in this instance, the formation and subsequent *C*-alkylation of

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the Kukhtin–Ramirez adduct outcompetes the otherwise anticipated *P*-alkylation of $P(NMe_2)_3$. Once formed, subsequent dissolution of **5** in water (0.05 M) at 60 °C for 2 h resulted in hydrolysis to complete a Barbier-like synthesis of alcohol **6** in 75% isolated yield (Scheme 1). The formation of alkene **7** as a minor product via elimination from **5** (vide infra) accounts for the balance of mass under these conditions.

The two-step, one-pot method is amenable to benzylic, allylic, and methyl electrophiles, generally providing isolable intermediate alkoxyphosphonium salts[10] that furnish alcohols **9**–**26** upon hydrolysis (Figure 2). The sequence is largely

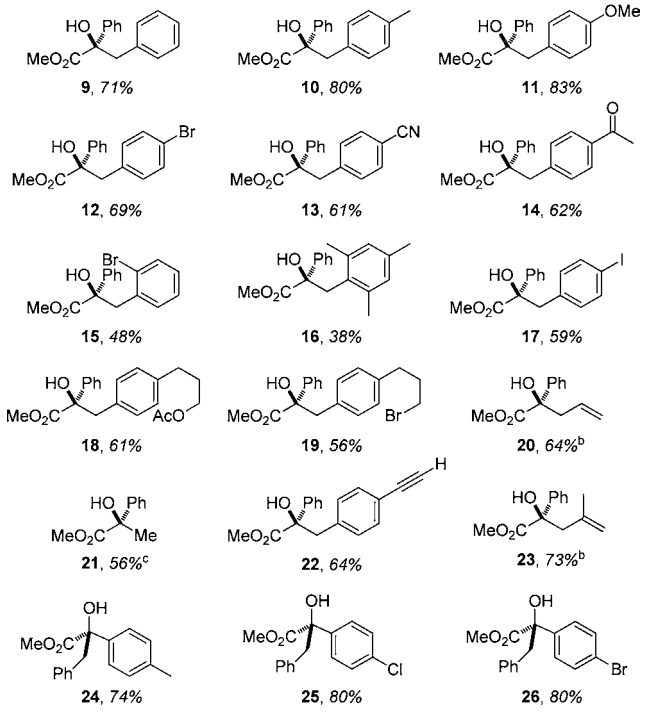
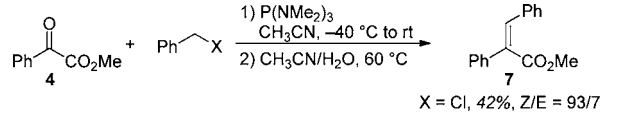


Figure 2. $P(NMe_2)_3$-mediated Barbier-coupling of methyl aroylformates with benzyl/allyl bromides.[a] [a] Reaction conditions: methyl aroylformate (2.2 mmol, 1.1 equiv), benzyl/allyl bromide (2.0 mmol, 1.0 equiv), and $P(NMe_2)_3$ (2.2 mmol, 1.1 equiv) in toluene (20 mL), −78 °C to rt, 2–3 h; decantation, then dissolution of alkoxyphosphonium salt in H_2O (40 mL), 60 °C for 2 h. Isolated yield based on benzyl/allyl bromide was reported. Yield of the elimination product was not determined. [b] Methyl benzoylformate (1.3 equiv) and $P(NMe_2)_3$ (1.3 equiv) were employed. [c] Methyl iodide was employed.

insensitive to electronic variation within the series of benzyl bromide electrophiles investigated, although lower yields are observed with sterically encumbered *ortho*-substituted benzyl bromides (**15** and **16**). As intimated above in the introduction, the fidelity of the Kukhtin–Ramirez redox reaction between the tricoordinate phosphorus reagent and α-dicarbonyl compound permits the use of electrophiles containing a variety of reactive functional groups, allowing straightforward access to alcohols bearing cyano (**13**), iodo (**17**), acetoxy (**18**), and ethynyl (**22**) moieties. In fact, the specificity of the Kukhtin–Ramirez trigger allows for selective reductive C–C alkylation even in the presence of pendant carbonyl (**14**) and alkyl bromide (**19**)[11] groups, illustrating the chemoselectivity of the mild closed-shell conditions. Substituted benzoylformate derivatives are similarly benzylated (**24**–**26**).

By modifying conditions in Scheme 1, the decomposition of alkoxyphosphonium salt **5** can be diverted to form *Z*-α,β-disubstituted acrylates[12] as the major product (Scheme 2). In this event, a one-pot olefination of methyl benzoylformate with

Scheme 2. Screening of Benzylating Reagents in the Olefination Reaction of Methyl Benzoylformate with $P(NMe_2)_3$



X = Cl, *42%*, Z/E = 93/7
X = Br, *84%*, Z/E = 93/7
X = OTf, *57%*, Z/E = 97/3

benzyl bromide can be achieved in wet acetonitrile giving **7** in 84% isolated yield (Scheme 2).[13] Benzyl bromide gives better overall yields than either benzyl chloride or tosylate electrophiles, although a marginally higher *Z*/*E* ratio was observed in the reaction using benzyl tosylate rather than benzyl halides (Scheme 2). Control reactions between independently synthesized benzylphosphonium **8** and methyl benzoylformate under the reaction conditions outlined in Scheme 2 are negative, eliminating the possible intervention of transient *P*-ylides in these olefination reactions. Similarly, the possible intervention of benzyl carbanionic intermediates through halophilic displacement[14] is inconsistent with the observation of product formation using benzyl triflate as an electrophile.

Additional examples of this nonylidic *P*-mediated olefination reaction are depicted in Figure 3. As in the $P(NMe_2)_3$-mediated Barbier-like reductive alkylation reaction (vide supra), *Z*-α,β-diaryl acrylates bearing diverse functionalities including bromo (**29** and **30**), acetoxyalkyl (**33**), bromoalkyl (**34**), cyano (**36**), acetyl (**37**), and iodo (**38**) on either α- or β-aromatic rings are accessible by this method in good yield and with excellent configurational selectivity. Furthermore, tetrasubstituted alkene **32** was obtained in 58% isolated yield from the reaction of (1-bromoethyl)benzene with methyl benzoylformate. The observed compatibility of a free hydroxy group (**35**) and an acidic terminal alkyne (**39**) reveals the quasi-neutral reaction conditions. Substituted benzoylformate derivatives are similarly olefinated (**42**–**44**).

The success of the above *P*-mediated C–C bond forming methods, which necessitates fast umpolung *C*-alkylation of an α-keto ester substrate in preference to a potential direct *P*-alkylation of $P(NMe_2)_3$, warrants additional mechanistic comment. Burgada has shown that the Kukhtin–Ramirez reaction of methyl aroylformates (**45**) with $P(NMe_2)_3$ is rapid at temperatures below −40 °C[15] and that the resulting 1:1 adduct **46** reversibly adds to an additional equivalent of **45** in aldol-like fashion to form a 2:1 adduct (**47**/**48**, Figure 4).[16] Burgada's findings suggest that the dynamic equilibrium **46** ⇌ **47**/**48** is stable in the absence of exogeneous reagents, only undergoing expulsion of hexamethylphosphoramide (HMPA) to generate epoxide **49** upon warming above −40 °C. However, in the presence of an alkylating agent as in this current study, the oxyphosphonium enolate intermediate **46** may be removed from the equilibrium via *C*-alkylation by reactive benzyl/allyl bromides to give the observed alkoxyphosphonium salt **50**. At such low temperatures, direct quaternization of $P(NMe_2)_3$ with benzyl bromide to give $(Me_2N)_3PBn^+Br^-$ (**8**)[17] evidently is not kinetically competitive.

Once formed, alkoxyphosphonium salt **50** evolves via either solvolysis or elimination as a function of the reaction medium. In view of the significant steric congestion at the reacting 3°

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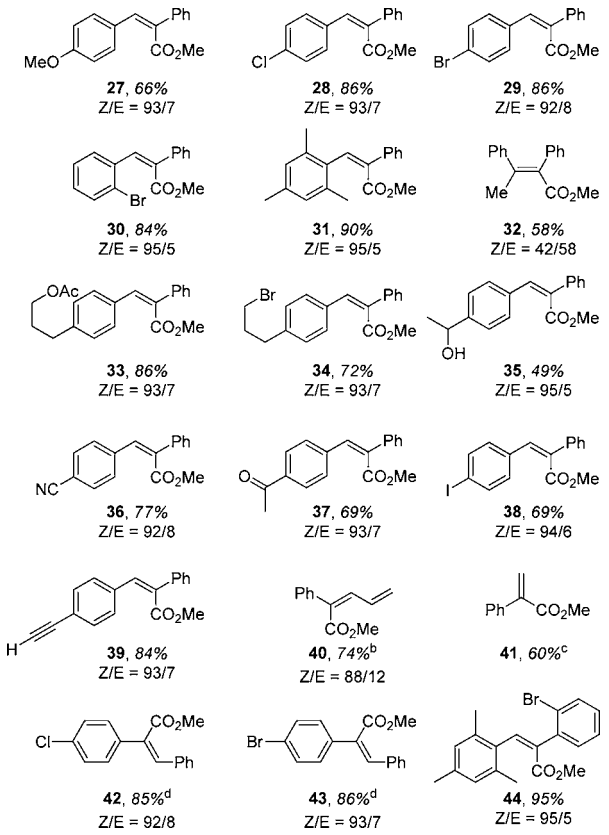


Figure 3. $P(NMe_2)_3$-mediated olefination reaction of methyl aroylformates with benzyl/allyl bromides[a] [a] Reaction conditions: methyl aroylformate (1.0 mmol, 1.0 equiv), benzyl/allyl bromide (1.1 mmol, 1.1 equiv), and $P(NMe_2)_3$ (1.1 mmol, 1.1 equiv) in CH_3CN (5 mL), −40 °C to rt, 1.5 h; added H_2O (0.10 mL), 60 °C for 2 h. Isolated yield based on methyl aroylformate was reported. *Z*/*E* ratio was determined by ^1H NMR analysis of the crude reaction mixture. [b] H_2O (0.15 mL). [c] Methyl iodide was employed, and no water was added before heating. [d] Heated for 3 h.

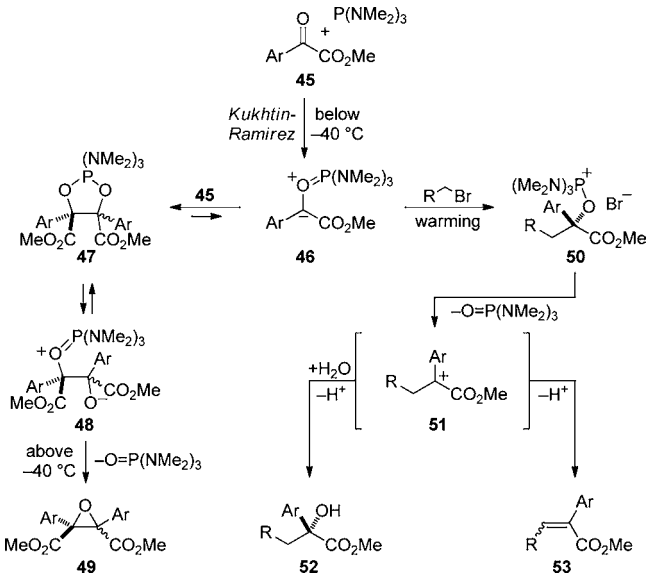
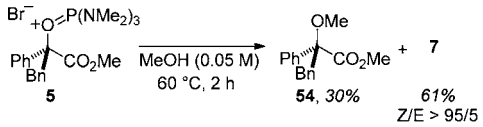


Figure 4. Possible mechanistic pathways.

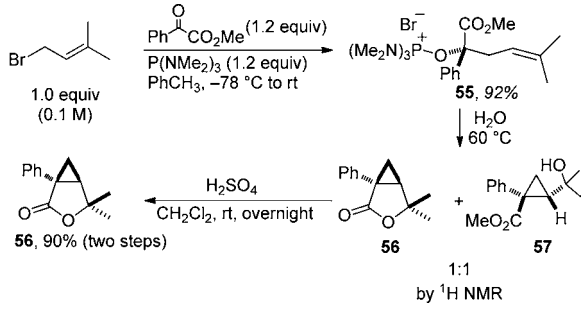
carbon center, both reaction manifolds most likely proceed via dissociative cationic pathways (viz. **51**)[18] involving initial loss of hexamethylphosphoramide. In accord with this notion, *α*-methoxy ester **54** was isolated in 30% yield by methanolysis of **5** (eq 1).



(1)

Further evidence for a cationic intermediate by loss of hexamethylphosphoramide from **5** is demonstrated by the observation of homoallylic participation[19] of a pendant prenyl group in **55** (prepared in 92% yield from the reaction of prenyl bromide and methyl benzoylformate), giving cyclopropanes **56** and **57** (Scheme 3). This mixture converges to **56** in excellent yield upon treatment with H_2SO_4 in dichloromethane.

Scheme 3. Carbocation Rearrangement to Cyclopropanes



In conclusion, we have described a $P(NMe_2)_3$-mediated umpolung alkylation of aroylformate-derived Kukhtin−Ramirez intermediates with alkyl halides. The reductive C−C bond forming reaction results in Barbier-like transformations or ylide-free olefinations depending on the choice of reaction medium. The key features of the reaction include (1) a synthesis of tertiary alkanols or *Z*-*α*,*β*-diaryl acrylates by C−C bond formation under mild conditions compatible with a wide range of functionality; (2) the use of a commercially available nonmetal reagent whose sole stoichiometric byproduct is water-soluble and can be eliminated by routine aqueous extraction; and (3) the closed-shell, two-electron umpolung of the carbonyl group, providing functional group compatibility and chemoselectivity. The selectivity of $P(NMe_2)_3$ toward *α*-dicarbonyl compounds evidenced here (in preference to other potent electrophiles including allylic and benzylic bromides) would suggest broader potential for development of reactions between the Kukhtin−Ramirez intermediates and other reactive electrophiles in a one-pot manner.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization data, and spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01784.

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Notes

The authors declare no competing financial interest.

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(9) Alkoxyphosphonium salt **5** is stable in the solid state and can be stored under a N_2 atmosphere at 5 °C for several months. It undergoes elimination in organic solution (cf. **7**, Scheme 2) at room temperature overnight.

(10) See Supporting Information for experimental details.

(11) Neither substitution nor elimination products of the alkyl bromide are observed.

(12) For alternative syntheses of α,β-disubstituted acrylates, see: (a) Zimmerman, H. E.; Ahramjian, L. *J. Am. Chem. Soc.* **1959**, *81*, 2086. (b) Greenman, K. L.; Van Vranken, D. L. *Tetrahedron* **2005**, *61*, 6438. (c) Chen, S.; Wang, J. *Chem. Commun.* **2008**, 4198. (d) Yu, W.-Y.; Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C. *Org. Lett.* **2009**, *11*, 469. (e) Xiao, Q.; Ma, J.; Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2009**, *11*, 4732. (f) Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 4506. (g) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236.

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