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A $C_{sp^3}-C_{sp^3}$ Bond Forming Reductive Condensation of α-Keto Esters and Enolizable Carbon Pronucleophiles

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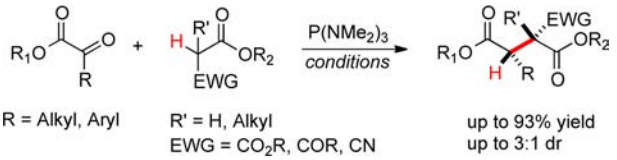
ABSTRACT



The preparation of densely functionalized unsymmetrical 1,4-dicarbonyl structural motifs by a phosphorus(III)-mediated reductive condensation of α-keto esters and enolizable carbon pronucleophiles is described. The reaction, which is initiated by Kukhtin–Ramirez addition of commercially available tris(dimethylamino)phosphine to the α-keto ester substrate, proceeds rapidly under mild conditions.

Highly functionalized unsymmetrical 1,4-dicarbonyl compounds are versatile intermediates in organic synthesis,[1] as well as common target motifs in natural products and biologically active small molecules.[2] Among the demonstrated approaches to 1,4-dicarbonyl compounds, the union of two C2 carbonyl fragments to forge the C_2-C_3 linkage is appealing in its convergency.[3] Synthetically, this bond construction is typically achieved via diverse prefunctionalized enolonium synthetic equivalents,[4] or alternatively via a two-electron oxidation of a preformed intermediate enolate.[5] New direct and mild methods for the formation of 1,4-dicarbonyls operating under alternative conditions might serve as a valuable complement to these traditional synthetic approaches.[6]

We recently reported a phosphorus(III)-mediated method for the synthesis of α-heterofunctionalized carbonyl derivatives via reductive condensation of α-keto esters and X–H pronucleophiles.[7] This method hinges on the

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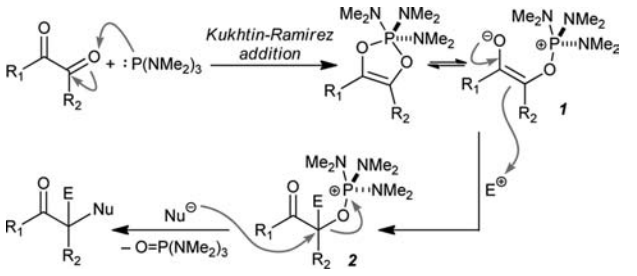
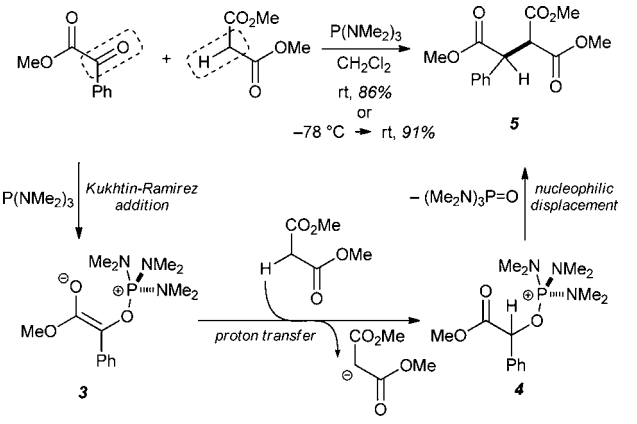
intermediacy of dipolar adducts **1** (Scheme 1) derived from the well-known Kukhtin–Ramirez addition of trivalent phosphorus reagents to 1,2-dicarbonyl compounds.[8] Adducts of the type **1** have been demonstrated to exhibit a rich reaction chemistry. For instance, treatment of **1** with electrophilic reagents gives rise to alkoxyphosphonium species **2**, which in turn may themselves then serve as electrophiles for nucleophilic displacement (Scheme 1).[7,9−13]

Scheme 1. Ambivalent Reactivity of Kukhtin–Ramirez Redox Adducts



Capitalizing on this reactivity trend, we considered the consequence of introducing a readily enolizable carbonyl derivative to Kukhtin–Ramirez adducts in solution (see Schemes 2, 3). In principle, a proton transfer yielding an alkoxyphosphonium ion **4** and the corresponding enolate could be envisioned.[14,15] Subsequent collapse of this ion pair via bond-forming nucleophilic displacement would then furnish a new C_{sp^3}–C_{sp^3} bond with expulsion of a phosphine oxide byproduct.[16] In sum, the overall reductive process would result in the preparation of versatile 1,4-dicarbonyl compounds by condensation of α-keto esters and carbon pronucleophiles under mild reductive conditions.

Scheme 2. P(III)-Mediated Reductive Coupling of Methyl Benzoylformate and Dimethyl Malonate



In a specific embodiment of the reaction sequence outlined above, the dropwise addition of tris(dimethylamino)-phosphine to a methylene chloride solution containing equimolar amounts of methyl benzoylformate and dimethyl malonate at ambient temperature gave the 1,4-dicarbonyl product of reductive condensation (**5**), isolated in 86% yield following extractive workup and chromatographic purification (Scheme 2). A modest increase in yield was obtained if the addition of tris(dimethylamino)-phosphine was initiated at −78 °C, with subsequent warming to rt over ∼30 min. Under these optimal conditions, **5** was isolated in 91% yield.

This C_{sp^3}–C_{sp^3} bond forming event is both rapid and high-yielding and proceeds under mild conditions in a single step and without elaborate prefunctionalization of the condensation partners.[17] Moreover, the use of commercially available tris(dimethylamino)phosphine as the promoter for this reaction offers a significant operational advantage since the water-soluble phosphoric triamide byproduct can be easily eliminated in workup by aqueous extraction.

An investigation of various α-keto esters revealed the versatility of this methodology (Scheme 3). The α-keto ester substrates for this survey are available in a single step from commercial compounds either by Friedel–Crafts

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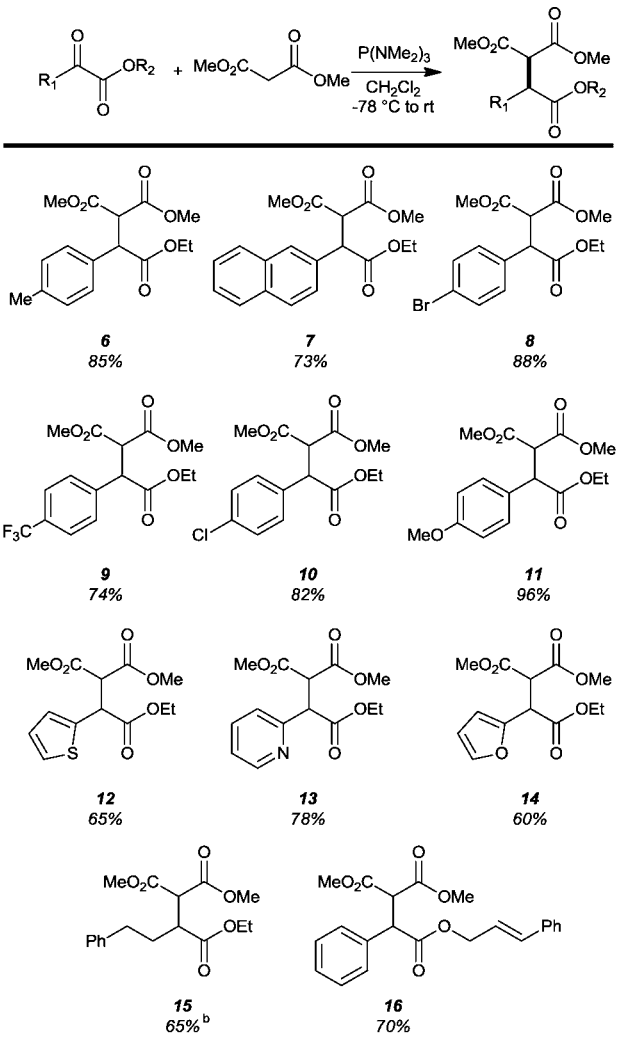
Scheme 3. P(III)-Mediated Reductive Coupling of Methyl Benzoyl Formate and Dimethyl Malonate[a]



[a] Reaction conditions: 1.0 mmol of α-keto ester substrate, 1.1 mmol of dimethyl malonate, 1.1 mmol of $P(NMe_2)_3$, CH_2Cl_2 (0.1 M), −78 °C to rt. Yields are reported for purified, isolated compounds. [b] Inverse addition: 1.0 mmol of α-keto ester substrate added to 1.5 mmol of dimethyl malonate and 1.1 mmol of $P(NMe_2)_3$, CH_2Cl_2 (0.1 M), rt.

acylation with ethyl oxalyl chloride[18] or by selective mono-addition of a Grignard reagent to ethyl oxalate.[19] Electronically diverse *para* substituted benzoylformate derivatives prepared in these ways react smoothly to give a series of 1,4-diesters (**6**, **8**−**11**). In this series, a mild preference for electron-rich substituents is apparent (compare **9** and **11**). This observation is consistent with the mechanism outlined in Scheme 2; both the proton transfer from the carbon pronucleophile to the Kukhtin−Ramirez adduct **3** and C−C bond forming nucleophilic displacement from alkoxyphosphonium **4** should be facilitated by electron-rich substrates.[20]

Heteroaromatic substrates, both π-excessive (furanyl **14**, thiophenyl **12**) and π-deficient (pyridinyl **13**), are well tolerated and give the corresponding products in moderate to good yield. Pendant unsaturated functionality (**16**) that might otherwise complicate enolate heterocoupling reactions proceeding via open-shell intermediates is fully compatible with the mild reaction conditions described here.[21]

Initial attempts to extend these standard reductive condensation conditions to alkyl substituted α-keto esters led to unsatisfactory yields of the desired C−C coupled product **15** (< 50%). Instead, epoxide products arising from reductive dimerization of the α-keto ester substrate predominated.[11] In order to overcome this limitation, a minor experimental modification was necessary: inverse addition of the alkyl α-keto ester to a rt solution of $P(NMe_2)_3$ and 1.5 equiv of dimethyl malonate restored the desired reductive condensation reactivity. Under these slightly modified conditions, the alkyl substituted succinate derivative **15** could be isolated in 65% yield.

The method may be readily extended to carbon pronucleophiles other than dimethyl malonate, offering significant opportunity for structural diversity (Scheme 4). 1,3-Diketone and 1,3-keto ester pronucleophiles exhibit reactivity in the reductive condensation reaction yielding the target 1,4-dicarbonyl products (**18** and **19**, respectively), although in both instances products arising from competitive *O*-alkylation of these pronucleophiles may be identified in the crude reaction mixtures. This issue of regioselectivity is eliminated in the case of nitrile substituted pronucleophiles. α-Cyano esters and amides couple smoothly with both alkyl (**23** and **24**) and aryl (**22** and **25**) substituted keto ester substrates under the $P(NMe_2)_3$-promoted conditions.

This method also proves useful for the construction of sterically congested $C_{sp^3}-C_{sp^3}$ bonds. For instance, the reductive condensation of methyl benzoylformate and dimethyl methylmalonate gives the α,α-disubstituted malonate derivative **26** in 55% yield.[22] Related reactivity with α-substituted cyanoacetate derivatives correspondingly gives products **27** and **28** bearing differentially substituted quaternary carbon centers in excellent yield.

The mild conditions and broad functional group compatibility of the $P(NMe_2)_3$-mediated reductive condensation method permits the synthesis of functionally diverse products with rich potential for further synthetic functionalization (Scheme 5). For instance, oxazolone **29** may be prepared by reductive condensation of methyl benzoylformate with **30** in 90% yield as a separable mixture of diastereomers. The major isomer of this functionalized

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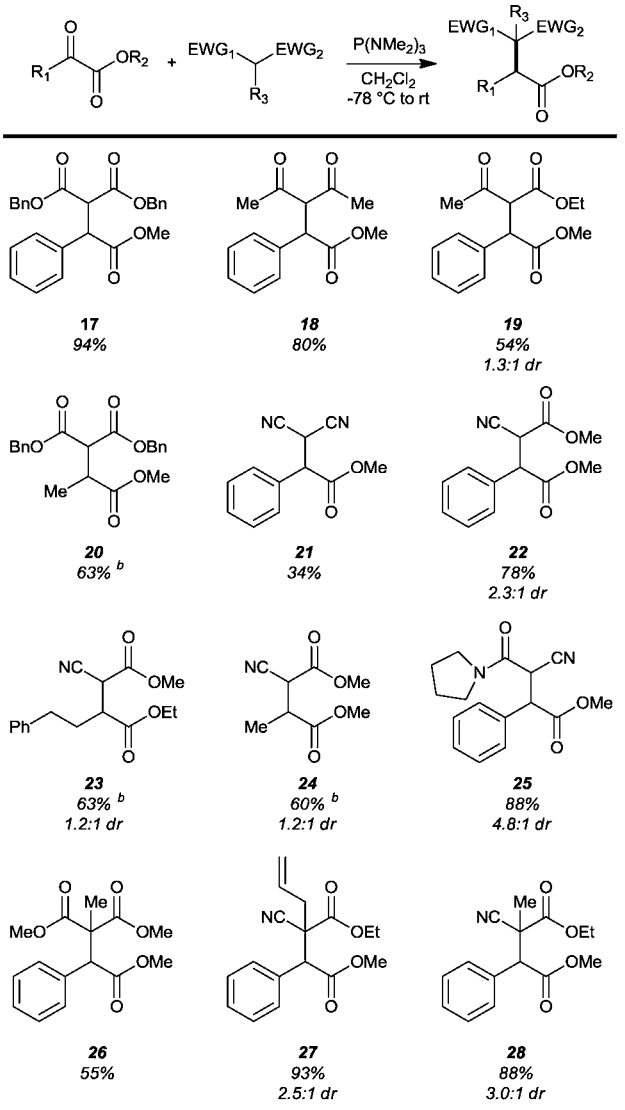
Scheme 4. P(III)-Mediated Reductive Coupling of α-Keto Esters and Various Carbon Pronucleophiles[a]

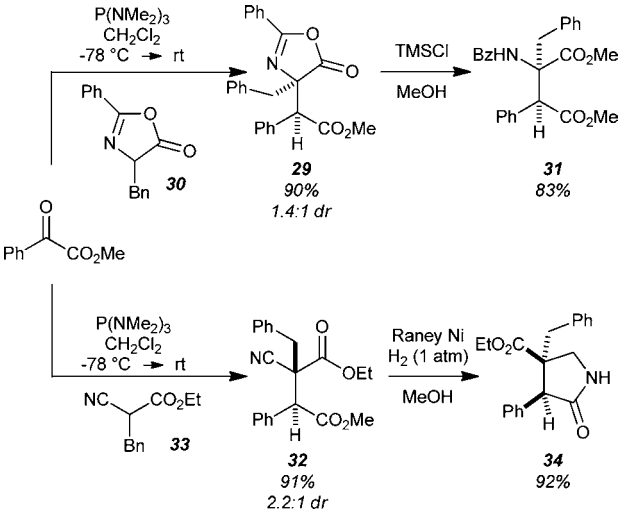


[a] Reaction conditions: 1.0 mmol of α-keto ester substrate, 1.1 mmol of dimethyl malonate, 1.1 mmol of $P(NMe_2)_3$, CH_2Cl_2 (0.1 M), −78 °C to rt. Yields are reported for purified, isolated compounds. [b] Inverse addition: 1.0 mmol of α-keto ester substrate added to 1.5 mmol of dimethyl malonate and 1.1 mmol of $P(NMe_2)_3$, CH_2Cl_2 (0.1 M), rt.

1,4-carbonyl product may be further derivatized to furnish densely substituted α-amino ester **31** by opening of the azlactone moiety.[23] Alternatively, selective nitrile hydrogenation of substituted cyanoacetate **32**, the product of reductive condensation of methyl benzoylformate and ethyl benzylcyanoacetate (**33**) isolated in 91% yield as a separable mixture of diastereomers, gives access to pyrrolidinone product **34**.

(23) Yields of **31** and **34** in Scheme 5 are reported for transformations on the major stereoisomer of **29** and **32**, respectively. Major diastereomers assigned by X-ray diffraction of single crystals.

Scheme 5. Synthetic Diversification of Reductive Condensation Products



In summary, we have demonstrated a new method for preparation of functionalized unsymmetrical 1,4-dicarbonyl compounds via a phosphorus(III)-mediated reductive condensation reaction. The method is characterized by the following attributes: (1) the reaction results in the formation of new $C_{sp^3}-C_{sp^3}$ bonds under mild conditions compatible with a wide range of functionality; (2) no stoichiometric preactivation (i.e., synthetic prefunctionalization, deprotonation with strong exogenous base) of either condensation partner is required; (3) readily available, bench stable reactants and a commercially available reagent are employed; and (4) the sole stoichiometric byproduct of the reaction is water-soluble and can be eliminated by routine aqueous extraction. We anticipate that the practicality and operational simplicity illustrated by these attributes should make this $C_{sp^3}-C_{sp^3}$ bond forming method a valuable complement to existing routes to unsymmetrical 1,4-dicarbonyl motifs. As a corollary, the results presented here further illustrate the synthetic potential of the Kukhtin−Ramirez adducts. Additional reaction development arising from the interception of Kukhtin−Ramirez intermediates is a current focus of ongoing investigation.

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Supporting Information Available. Synthetic procedures for the preparation of starting materials and products, analytical data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.