Carbenoids

DOI: 10.1002/anie.201205604

A Nonmetal Approach to α-Heterofunctionalized Carbonyl Derivatives by Formal Reductive X–H Insertion**

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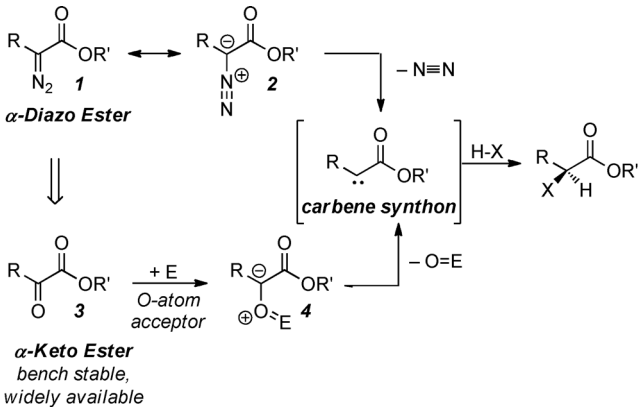
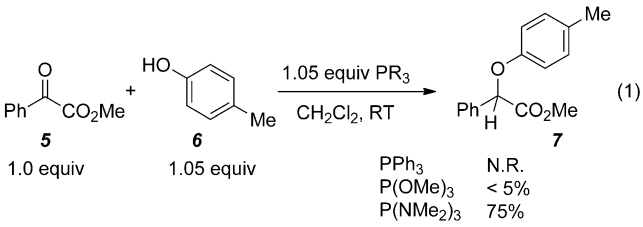
Synthetic methods leading to the formation of α-heterofunctionalized carbonyl derivatives are valuable for the preparation of important molecular targets.[1] Among the varied synthetic approaches to these compounds,[2] the direct functionalization of an X–H bond by insertion of a carbene equivalent has proven expedient and versatile.[3–5] In practice, the required carbene synthons may be accessed by metal-catalyzed decomposition of α-diazo compounds.[6] Despite the utility of this approach, its appeal is tempered by the fact that only a modest number of diazo compounds are commercially available, a circumstance that is due in large part to hazards associated with preparation, isolation, and storage of these compounds.[7] Consequently, alternative strategies for the direct X–H functionalization transformation that retain the power and simplicity of the diazo decomposition approach, but broaden access to starting materials, would be desirable.

In considering alternative carbene synthetic equivalents,[8] we recognized that α-diazo carbonyl compounds are routinely prepared from the corresponding α-keto carbonyl derivative.[9] Consequently, we considered the possibility that this class of readily accessible and bench-stable compounds might be utilized directly en route to carbene-like reactivity, thereby obviating the intermediacy of unstable diazo compounds. We envisioned that exposure of α-keto ester **3** to a suitable oxygen-atom acceptor would furnish a dipolar structure of the type **4**, which by analogy to α-diazo ester resonance contributor **2** might serve as a synthetic equivalent of a carbenoid.[10] In a practical sense, intermediates of the type **4** may be accessed by the well-known Kukhtin–Ramirez redox condensation of 1,2-dicarbonyl compounds with trivalent phosphorus derivatives (E = PR_3; Scheme 1).[11] Indeed, the intermediacy of these adducts in various epoxide- and cyclopropane-forming procedures[12,13] lends support for their formal carbene equivalency, and isolated evidence suggests a further potential for X–H functionalization reactivity.[14] Herein, we realize this potential in an operationally simple, metal-free method for the preparation of α-heterofunctionalized carbonyl derivatives by direct reductive X–H functionalization employing readily available and bench-stable coupling components.



Scheme 1. Synthetic routes to access carbene synthons.

An investigation was initiated using the direct reductive coupling of methyl benzoylformate (**5**) and *p*-cresol (**6**) mediated by oxygen-atom acceptors as a demonstration reaction [Eq. (1)]. In accord with the hypothesis outlined



above, we have found the addition of tris(dimethylamino)-phosphorus to a solution of **5** and **6** results in direct reductive O–H functionalization, leading to the formation of the α-phenoxy ester **7** in good yield.[15] Neither phosphines (PPh_3) nor phosphites ($P(OMe)_3$) are similarly reactive under otherwise identical conditions,[16] an observation that may be attributed to inferior P=O bond enthalpies.[17]

In terms of scope, the coupling method tolerates a range of electronically and sterically diverse α-keto ester substrates (Table 1). Both electron-rich (**9**) and electron-deficient (**10**) benzoylformate derivatives serve as viable substrates for coupling, and the series of *p*-halogenated *O*-aryl mandelate derivatives (**11**–**13**) may be prepared. Aryl substitution of the ketone is not strictly required for efficient reaction; alkyl-substituted keto ester substrates yield the expected corresponding α-phenoxy ester product in good yield. For example, methyl (**14**), primary alkyl (**15**), and secondary alkyl substituents (**16**) are all well-tolerated.

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[**] We thank the Pennsylvania State University for financial support of this research.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201205604.

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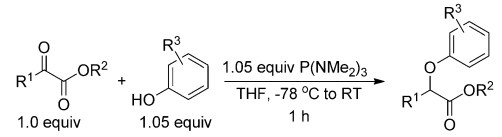
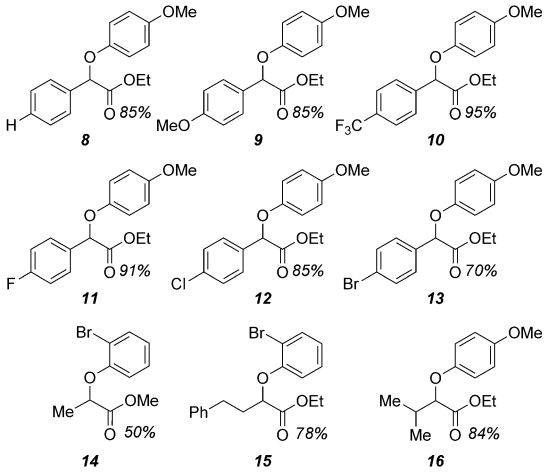
Table 1: Scope of α-keto ester substrates for reductive O–H functionalization.[a]



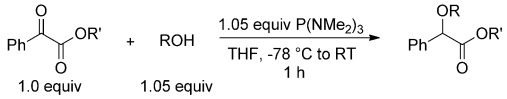


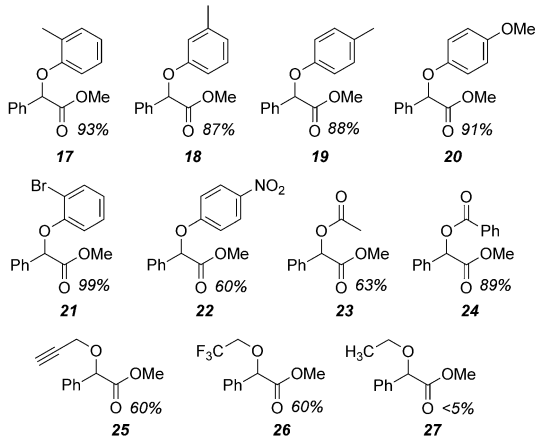
[a] Yields of isolated product.

With respect to the protic oxygen coupling partner, the method also proves to be quite versatile (Table 2). The suite of cresol regioisomers all react smoothly to provide the corresponding α-aryloxy esters in uniformly high yields (**17**–**19**). Modulation of the electronic character of the phenol derivative has only a modest influence on the reaction outcome; the reactivity of electron-rich phenols (4-methoxyphenol) is exemplary (**20**), whereas yields are modestly diminished by electron-withdrawing substitution (**22**). The method is not limited to phenolic O–H functionalization; indeed, carboxylic acids undergo smooth coupling to give α-acetoxylated esters (**23**, **24**) in good yields. The method can also be extended to aliphatic alcohols, although the reaction with these nucleophiles appears somewhat less general. For instance, propargyl alcohol and trifluoroethanol both undergo functionalization under standard conditions to give the anticipated products **25** and **26**, respectively. However, only trace amounts compound **27** can be observed when ethanol is employed as a coupling partner.[18,19] This observed reactivity for aliphatic alcohols correlates with pK_a,[20] suggesting a degree of O–H bond heterolysis in the coupling event (see below).

The coupling method can be successfully applied to the direct X–H functionalization of other heteroatomic nucleophiles (Table 3). Sulfonyl-protected amine derivatives undergo smooth coupling to give protected phenylglycine (**28**) and alanine (**29**) derivatives in good yield. This method thus permits the direct synthesis of diverse *N*-substituted α-amino ester products by reaction of *N*-aryl (**30**) and *N*-alkyl (**31**–**33**) sulfonamides. Protic *N*-heterocyclic compounds can also be employed in the coupling; for example, phthalimide (**34**), imidazole (**35**), and pyrazole (**36**) all lead to the coupling products.

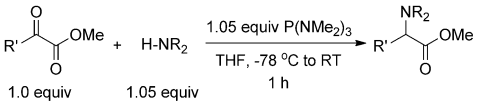
Table 2: Scope of nucleophiles for reductive O–H functionalization.[a]

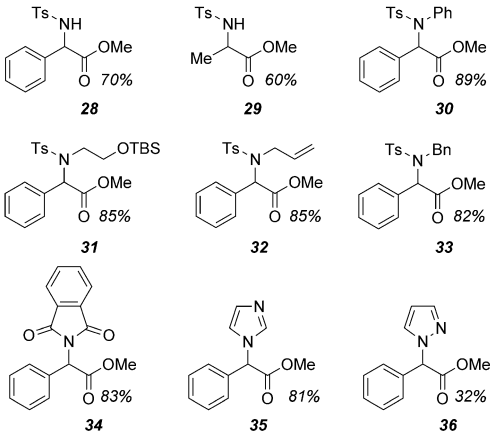




[a] Yields of isolated product.

Table 3: Scope of nucleophiles for reductive N–H functionalization.[a]





[a] Yields of isolated product.

Mechanistically, we believe the reductive X–H functionalization transformation is initiated by Kukhtin–Ramirez condensation of tris(dimethylamino)phosphorus with the α-keto ester substrate (Scheme 2).[11] Addition of the aminophosphine reagent to the carbonyl oxygen of the keto ester substrate could give a 1,3-dipolar intermediate (**37**), which would experience stabilization as oxyphosphonium enolate resonance structure **37′** or dioxaphospholene valence isomer **38**; features governing partitioning of the type **37**–**38** have been investigated.[21] Subsequent X–H functionalization could then evolve along two distinct mechanistic pathways. Loss of tris(dimethylamino)phosphine oxide could reveal

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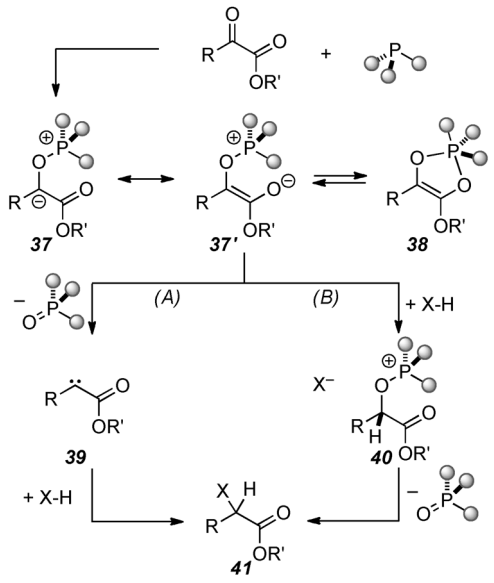
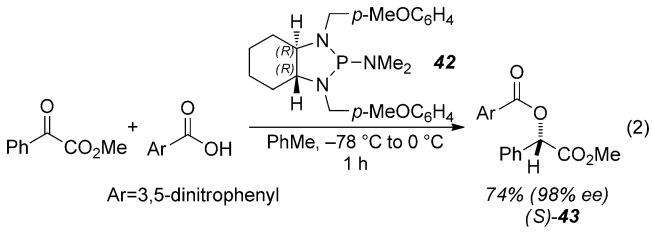


Scheme 2. Possible mechanisms for X–H functionalization.

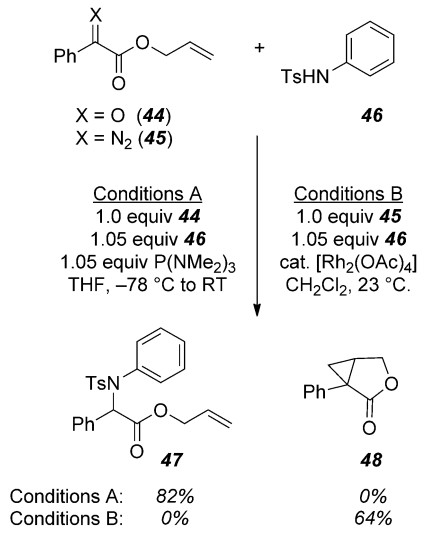
a free carbene intermediate (**39**) in solution (Scheme 2, pathway A),[21] the capture of which by X–H bond insertion would lead to product **41**. Alternatively, adducts **37**–**38** may be intercepted by proton transfer from the pronucleophile (X–H) to give alkoxyphosphonium intermediate **40** (pathway B), which could then undergo nucleophilic displacement to furnish product.[22–24]

In principle, the foregoing mechanistic possibilities may be differentiated by stereochemical experiments employing homochiral phosphorus reagents. In this analysis, use of a homochiral phosphorus reagent would desymmetrize key intermediates **37**–**38**. In the event a stepwise polar mechanism were operative, facially selective protonation to give stereodefined alkoxyphosphonium **40** could be envisioned, and subsequent stereospecific displacement of the phosphoric triamide leaving group would yield stereodefined product **41**. By contrast, if a free carbene were generated in accord with pathway A, a stereoselective X–H functionalization would not be expected.

As depicted in Equation (2), we have found that reductive coupling of methyl benzoylformate and benzoic acid derivatives employing homochiral diazaphospholidine (*R*,*R*)-**42**[25] is indeed stereoselective. The reductive coupling gives *O*-acyl mandelate derivative (*S*)-**43** with good yield and excellent stereoselectivity.[26]



In light of the observed stereoselectivity, we regard as remote the possibility that genuine carbene intermediates are formed (pathway A) under our conditions; instead, carbenoid reactivity evinced by a stepwise, polar mechanism (pathway B) would appear to be most consistent with the observed outcome. This mechanism, in which proton transfer precedes α-C–X bond formation, distinguishes our metal-free method from X–H bond functionalization by metal carbenoids, where proton transfer follows α-C–X bond formation.[27] The complementarity in electronic character implied by this mechanistic distinction (species **37**–**38** are nucleophilic, whereas metal carbenoids are electrophilic[28]), suggests the potential for differential application of these two classes of reactive intermediates (Scheme 3). Specifically, N–H functionalization prevails when a solution of allyl benzoylformate (**44**) and *N*-phenyl sulfonamide **46** are exposed to tris(dimethylamino)phosphorus under our optimized conditions; product **47** is selectively produced in 82% yield, and cyclopropane **48** is not observed. By contrast, only **48** is produced from the addition of rhodium acetate to a methylene chloride solution of diazo substrate **45** and sulfonamide **46**, indicating that intramolecular olefin trapping effectively competes with intermolecular N–H insertion for the electrophilic metal carbenoid.



Scheme 3. Intermolecular N–H functionalization versus intramolecular cyclopropanation.

In conclusion, we have described a mild and direct method the coupling of α-keto esters and protic oxygen and nitrogen pronucleophiles for the synthesis of valuable α-heterofunctionalized carbonyl derivatives. The reaction effects a direct reductive X–H functionalization by employing nonmetal reagents and substrates that are readily available and bench-stable. Consequently, neither prefunctionalization of the coupling partners nor the intermediacy of highly reactive diazo compounds is required. Additional applications of the reactive system composed of α-dicarbonyl compounds and oxygen-atom acceptors for the controlled access to nucleophilic carbene synthons are currently under investigation.

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Experimental Section

Representative procedure: In a dried 25 mL round bottom flask, methyl benzoylformate (164 mg, 1.0 mmol) and *p*-cresol (113 mg, 1.05 mmol) were dissolved in dry tetrahydrofuran (10 mL, 0.1M) and the solution was cooled to −78 °C. Tris(dimethylamino)phosphine (0.20 mL, 1.05 mmol) was added dropwise by a syringe. Upon complete addition of the aminophosphine, the cooling bath was removed and the solution was allowed to warm to ambient temperature over the course of 1 h. Once the starting material was consumed (monitored by TLC), the reaction mixture was concentrated to a residue and redissolved in 50 mL of ethyl acetate. The organic layer was washed sequentially with 10% NaOH and brine, then dried (Na_2SO_4) and concentrated. The product was isolated in 88% yield (225 mg) after purification by column chromatography (silica gel, 1:10 EtOAc/hexanes as eluent).

Received: July 14, 2012
Published online: September 20, 2012

Keywords: carbenoids · insertion · ketones · phosphorus · synthetic methods

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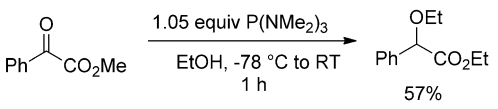

[20] The following pK_a values have been determined in H_2O at 25 °C: pK_a(trifluoroethanol) 12.4, pK_a(propargyl alcohol) 13.6, pK_a-

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