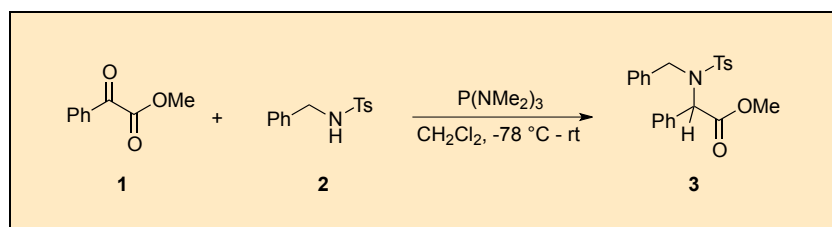


## Phosphorus(III)-Mediated Reductive Condensation of $\alpha$ -Keto Esters and Protic Pronucleophiles

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### Procedure

A. *Methyl 2-(N-Benzyl-4-Methylphenylsulfonamido)-2-Phenylacetate (3)*. 4-Methyl-N-(phenylmethyl)benzenesulfonamide (2) (8.49 g, 32.5 mmol, 1.1 equiv) is placed in an oven-dried, 1-L 3-necked round-bottomed flask equipped with a magnetic stir bar (1.5 × 3.5 cm, Teflon-coated, egg-shaped). The center neck of the reaction flask is fitted with a rubber septum-capped 250-mL pressure-equalizing addition funnel. One of the side necks is fitted with a rubber septum and the other is fitted with a nitrogen inlet (Figure 1). The reaction vessel is then purged with nitrogen atmosphere by three evacuation-backfill cycles (Note 1). Dry dichloromethane (296 mL, 0.1 M) is added to the round-bottomed flask via cannula transfer from an oven-dried 1-L Schlenk flask (Note 2). Methyl benzoylformate (1) (4.20 mL, 4.85 g, 29.6 mmol, 1.0 equiv) is added to the solution through the side neck (Note 3). The addition funnel is then charged with tris(dimethylamino)phosphine (5.90 mL, 5.30 g, 32.5 mmol, 1.1 equiv) through the septum on top (Note 4). Dichloromethane (33 mL) is added to the addition funnel in the same way

using a 60-mL syringe and an oven-dried steel needle. The reaction flask is cooled to  $-78\text{ }^{\circ}\text{C}$  with a dry ice-acetone bath in an appropriately sized cooling vessel (Note 5). The tris(dimethylamino)phosphine solution is added dropwise to the flask over 20–30 min while stirring (Notes 6 and 7). Upon complete addition of the tris(dimethylamino)phosphine solution, the cooling bath is removed and the reaction mixture is stirred for 2 h, during which time it warms to ambient temperature (Note 8).



**Figure 1.** Reaction Set-up

When the reaction reaches completion as determined by TLC (Note 9), the dropping funnel is removed and distilled water (300 mL) is added to the reaction mixture in one portion. The biphasic mixture is then transferred to a 1-L separatory funnel (Note 10). The organic layer is separated, washed with saturated aqueous sodium chloride solution ( $3 \times 400\text{ mL}$ ), dried over anhydrous sodium sulfate (150 g) for 15 min (Note 11). The sodium sulfate

is filtered and the solution is concentrated in vacuo using a rotary evaporator (ca. 100 mmHg, water bath temperature 30 °C). The crude residue is purified by silica gel flash column chromatography using EtOAc and hexanes as eluent (Notes 12, 13, 14 and 15), yielding the title compound as an air and moisture stable white amorphous solid (10.7 g, 88%) (Notes 16 and 17) (Figure 2).

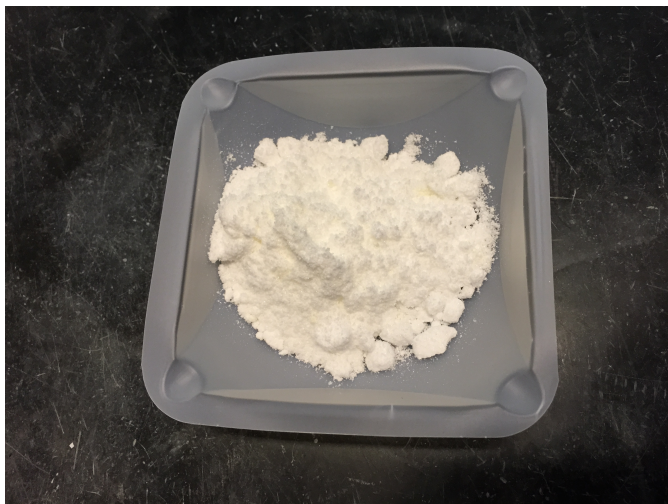
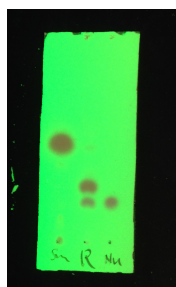


Figure 2. Amorphous white product

## Notes

1. 4-Methyl-*N*-(phenylmethyl)benzenesulfonamide was synthesized according to the known procedure: Coste, A.; Couty, F.; Evano, G. *Org. Synth.* **2010**, 87, 231.
2. Dichloromethane was purchased from Fischer Scientific (D138-4) and degassed by bubbling argon for 1.5 h before passing through an activated alumina column using a Glass Contour solvent drying system. The solvent was collected in an oven-dried 1-L Schlenk flask, which had been purged with argon atmosphere by three evacuation-backfill cycles.
3. Methyl benzoylformate (>97.0%) was purchased from TCI and used as received.

4. Tris(dimethylamino)phosphine (97%) was purchased from Alfa Aesar and used as received.
5. 4-Methyl-*N*-(phenylmethyl)benzenesulfonamide may not be completely dissolved at this temperature.
6. The rate of the addition was held at approximately 2 drops per second.
7. The mixture was stirred at 600 rpm throughout the reaction.
8. The reaction should remain colorless to faint yellow. A bright yellow color usually indicates the formation of side products.
9. Thin layer chromatograph was performed on silica gel 60 F<sub>254</sub> TLC plate (EMD Millipore TLC Silica Gel 60 Glass Plates, purchased from Fischer Scientific) with 1:6 EtOAc:hexanes as eluent. The following *R<sub>f</sub>* values were observed (visualized under 254 nm UV light): *R<sub>f</sub>* (methyl benzoylformate): 0.40; *R<sub>f</sub>* (4-methyl-*N*-(phenylmethyl)benzenesulfonamide): 0.14; *R<sub>f</sub>* (product): 0.22. Picture of TLC plate is shown below (left lane: methyl benzoylformate; middle lane: reaction mixture; right lane: 4-methyl-*N*-(phenylmethyl)benzenesulfonamide) (Figure 3).



**Figure 3.** Image of TLC Analysis

10. Extractions should be performed carefully, since HMPA is produced as a byproduct of the reaction.
11. Sodium chloride and sodium sulfate were purchased from VWR and used as received.
12. Silica gel (230-400 mesh) was purchased from SiliCycle and used as received.
13. Ethyl acetate and hexanes were purchased from Fischer Scientific and used as received.
14. Dichloromethane (5 mL) was added to the crude mixture. The crude product was loaded onto a column packed with silica gel slurry in 1:10 EtOAc:hexanes. Column is 8 cm in diameter, height of silica gel is



- 27 cm. After 1 L of initial elution with 1:10 EtOAc:hexanes, 1:8 EtOAc:hexanes (1,800 mL), 1:7 EtOAc:hexanes (1,600 mL) and 1:6 EtOAc:hexanes (2,500 mL) were collected in 90 mL fractions.
15. The product was isolated as a white amorphous solid and had the following spectral characteristics:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.44 (s, 3 H), 3.60 (s, 3 H), 4.42 (d,  $J$  = 16.2 Hz, 1 H), 4.65 (d,  $J$  = 16.2 Hz, 1 H), 5.80 (s, 1 H), 6.87 (dd,  $J$  = 7.7, 1.8 Hz, 2 H), 7.01–7.06 (m, 3 H), 7.10–7.15 (m, 2 H), 7.17–7.23 (m, 3 H), 7.25–7.28 (m, 2 H), 7.61–7.65 (m, 2 H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 21.7, 49.4, 52.3, 63.2, 126.8, 127.5, 127.8, 128.0, 128.8, 128.9, 129.4, 129.6, 133.5, 136.9, 137.5, 143.6, 170.6. IR (neat film, NaCl): 3031, 2951, 1747, 1598, 1496, 1454, 1437, 1342, 1206, 1162, 1091, 1029, 932, 814, 747, 696, 661  $\text{cm}^{-1}$ . HRMS (MM: ESI/APCI):  $m/z$  calcd for  $\text{C}_{23}\text{H}_{24}\text{NO}_4\text{S}$   $[\text{M}+\text{H}]^+$ : 410.1426. Found: 410.1421. Anal. Calcd for  $\text{C}_{23}\text{H}_{23}\text{NO}_4\text{S}$ : C, 67.46; H, 5.66; N, 3.42; O, 15.63; S, 7.83. Found: C, 67.40; H, 5.70; N, 3.39; O, 15.73; S, 7.85.
16. The melting point of the solid was determined to be 84–86 °C. The submitters report a mp of 96–98 °C. All other characterization data was identical for products produced by the checkers and the submitters.
17. Reaction run on one-half scale resulted in a white amorphous solid (5.22 g, 85% yield).

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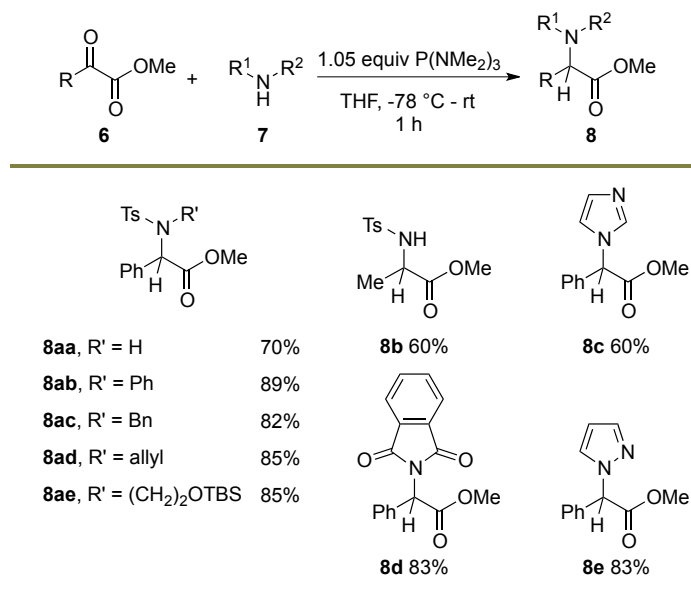
## Discussion

Phosphorus(III) reagents are known to undergo reaction with 1,2-dicarbonyl compounds to give adducts of formal *P*-addition to the carbonyl oxygen (Kukhtin-Ramirez reaction).<sup>2</sup> We have shown that these Kukhtin-Ramirez adducts further react to incorporate a range of *N*-, *O*-, and *C*-based protic pronucleophiles with expulsion of a phosphine oxide by-product.<sup>3,4</sup> The process likely proceeds in stepwise fashion, initiated by proton transfer from the protic pronucleophile to the Kukhtin-Ramirez adduct, followed by Arbuzov-like displacement of the phosphine oxide leaving group. This reaction sequence therefore represents a convenient one pot process for access to a range of  $\alpha$ -functionalized carbonyl compounds from readily available reagents and precursors.<sup>3,4</sup>

The synthetic method is exemplified in the above procedure, which demonstrates the synthesis of methyl 2-(*N*-benzyl-4-methylphenylsulfonamido)-2-phenylacetate (**3**), an  $\alpha$ -amino ester derivative.<sup>5</sup> By direct reductive construction of the  $\alpha$ -C-N bond, our approach takes advantage of the wide available  $\alpha$ -keto esters as starting materials, and provides an operationally simple and chemoselective alternative to transamination and reductive amination strategies.<sup>6,7</sup> Furthermore, since this method does not involve the intermediacy of imine equivalents, useful C-N bonds from *N*-pronucleophiles that do not form

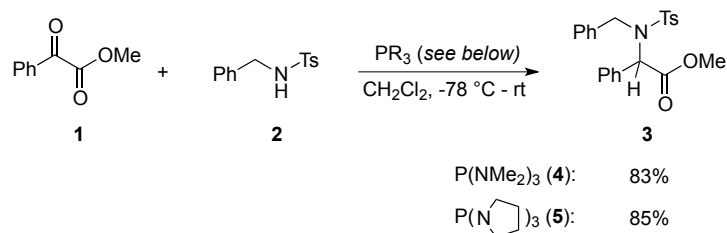
imines (e.g. azoles) can be successfully synthesized using this method (Table 1).<sup>7</sup>

Table 1. Scope of the phosphorus(III)-mediated  $\alpha$ -amino ester synthesis<sup>a</sup>



<sup>a</sup> Yields under literature reported conditions<sup>2</sup>

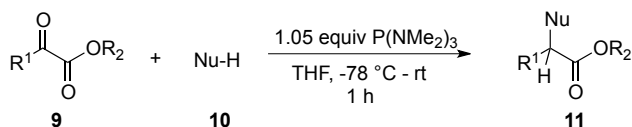
The reaction is tolerant of a range of solvents ( $CH_2Cl_2$ , THF, PhMe), but the use of dichloromethane reliably provides the highest yields and streamlines the aqueous workup on the laboratory scale. The use of commercially available  $P(NMe_2)_3$  results in the formation of  $O=P(NMe_2)_3$  (i.e. HMPA), a water soluble byproduct that is readily eliminated by aqueous extraction. In view of potential handling concerns resulting from the toxicity of HMPA, we note that the use of alternative phosphorous triamide reagents, specifically tris(1-pyrrolidiny)phosphine (which generates a less toxic phosphorus(V) oxide by-product), provide similarly satisfactory results (Scheme 1, 1.8 mmol scale).<sup>8</sup>



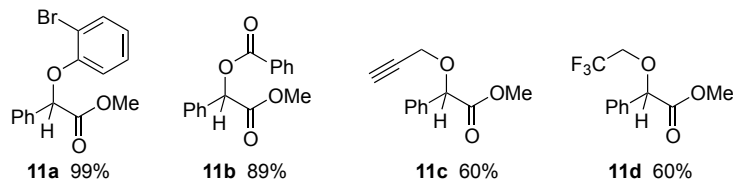
**Scheme 1. Phosphorus(III)-mediated synthesis of  $\alpha$ -amino esters.**

As noted in our previous studies, the scope of the reaction includes a diverse of *O*-based (phenols, carboxylic acids and some alcohols) and *C*-based (readily enolizable 1,3-dicarbonyls and related derivatives) protic pronucleophiles. The selection of protic pronucleophile is bracketed by  $\text{pK}_a$ , with only those species capable of proton transfer to the Kukhtin-Ramirez adduct ( $\text{pK}_a$  ca. 25-27 in DMSO) being reactive under these conditions (Table 2).

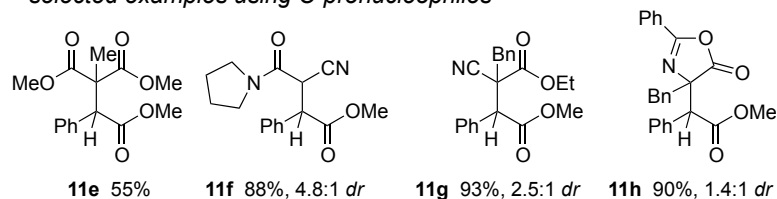
**Table 2. Additional examples of phosphorus(III)-mediate carbonyl functionalization with *O*- and *C*-pronucleophiles**



*selected examples using O-pronucleophiles*



*selected examples using C-pronucleophiles*



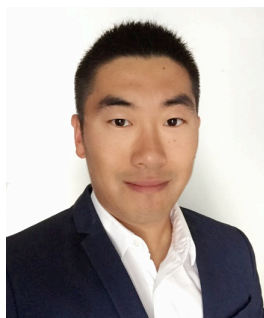
## References

1. Department of Chemistry, Pennsylvania State University, University Park, PA 16802, radosevich@psu.edu. We thank NIGMS (GM114547), Alfred P. Sloan Foundation, and the Pennsylvania State University for funding.
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## Appendix

### Chemical Abstracts Nomenclature (Registry Number)

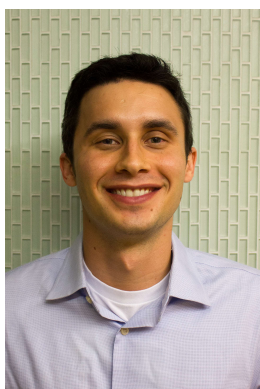
4-Methyl-*N*-(phenylmethyl)benzenesulfonamide: Benzenesulfonamide, 4-methyl-*N*-(phenylmethyl)-; (1576-37-0)  
 Dichloromethane: Methane, dichloro-; (75-09-2)  
 Methyl benzoylformate: Benzeneacetic acid,  $\alpha$ -oxo, methyl ester; (15206-55-0)  
 Tris(dimethylamino)phosphine: Phosphorus triamide, *N,N,N,N',N',N'*-hexamethyl-; (1608-26-0)  
 Sodium Chloride: sodium chloride; (7647-14-5)  
 Sodium Sulfate: sulfuric acid sodium salt (1:2); (7757-82-6)



Wei Zhao is from Jinan, Shandong Province, P. R. China. He completed his BSc at Xiamen University, working with Prof. Pei-Qiang Huang and Prof. Xiao Zheng. In fall 2010 he joined Penn State Chemistry working with Prof. Alexander Radosevich. He is now a senior graduate student with research focused on redox catalysis at geometrically constrained organophosphorus compounds.



Alex Radosevich is from Waukegan, IL and received his B.S. from Notre Dame (2002). He obtained a Ph.D. from UC Berkeley (2007) working with Prof. Dean Toste. Following postdoctoral research at MIT with Prof. Dan Nocera, he joined the department of chemistry at Penn State in 2010 as an assistant professor, where his research has focused on the design, development, and implementation of new synthetic methodology.



Jared Moore is from Libertyville, IL and attended Cal Poly, San Luis Obispo where he received his B.S. (2009). He obtained a Ph.D. from UC Davis in 2014 in the laboratory of Prof. Jared Shaw, where his research was focused on the development of new synthetic methods. Jared is currently an NIH postdoctoral research fellow at Caltech where he investigates the total synthesis of meroterpene natural products with Prof. Brian M. Stoltz.



