

SEPTEMBER
23-27TH
2024

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ON ORGANIC SYNTHESIS
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Redox-Neutral Stereospecific Deoxyalkylation of Alcohols Enabled by an Interrupted Appel Reaction

Izzy L. Wood^{1*} and Ross M. Denton¹

¹) Carbon Neutral Laboratories, University of Nottingham, 6 Triumph Rd, Lenton, Nottingham NG7 2GA

*e-mail: pcyiw@nottingham.ac.uk

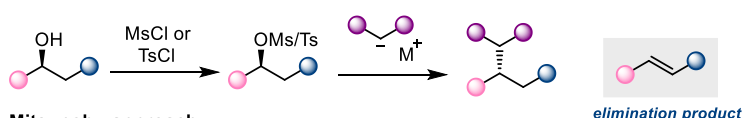
Keywords: organophosphorus chemistry, stereoselective synthesis, alkylation.

ABSTRACT

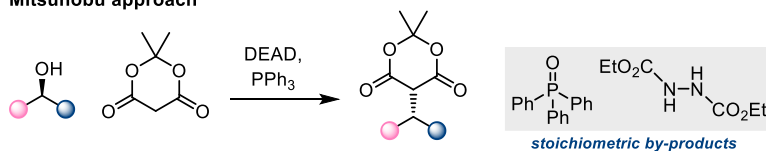
Strategies to forge sp^3 - sp^3 carbon linkages are integral to the field of synthetic organic chemistry.¹ Alcohols are abundant and generally easy to handle in the laboratory which makes them ideal partners for cross-coupling and alkylation.² Unfortunately, there are limited methods for direct, stereospecific, nucleophilic substitution of alcohols with carbon nucleophiles, despite the advantage of avoiding a discrete activation step.³ Mitsunobu-based protocols using Brønsted acidic carbon nucleophiles have been shown to be efficient, yet often require the use of high energy diazodicarboxylates as oxidants, which limits their application.⁴⁻⁸

We have developed a direct, redox-neutral phosphorus(V)-mediated approach in which alkoxyphosphonium intermediates, generated from phosphine oxides, undergo coupling with exogenous carbon nucleophiles. This process is driven by an Interrupted Appel reaction, eliminates the need for hazardous oxidants, and allows for recycling of the phosphine oxide, the waste product of conventional approaches.⁸

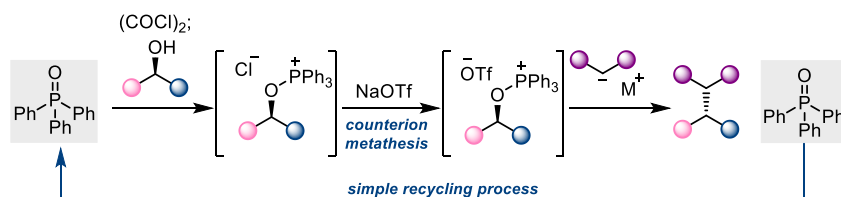
Pre-activation of alcohols



Mitsunobu approach



This work: Redox-neutral deoxyalkylation



ACKNOWLEDGEMENTS

We acknowledge the EPSRC for funding this work.

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