Organic Synthesis Using the Mobile Activating Group, Diphenylphosphinoyl

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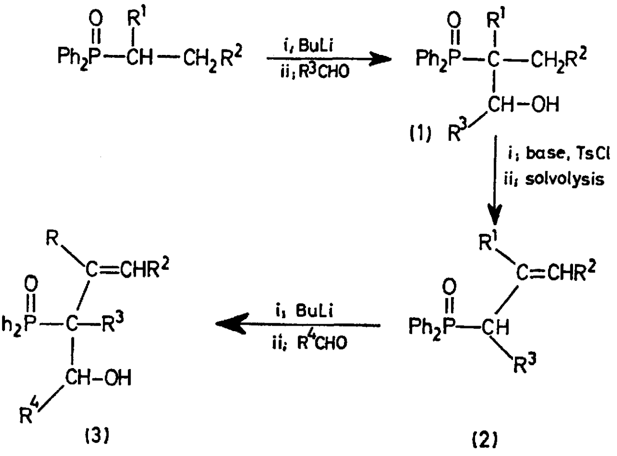
Summary The diphenylphosphinoyl group, $Ph_2P(O)$, activates a series of carbon–carbon bond forming reactions from successive carbon atoms in an organic synthesis by migration along the developing carbon framework.

ORGANIC synthesis involves the formation of carbon–carbon bonds, often by reaction between electrophilic and nucleophilic carbon atoms, followed by the manipulation of functional groups and the repetition of these processes until the target molecule is complete.[1] The nucleophilic carbon atom is often activated by a functional group (carbonyl etc.) which is removed or transformed once its job is done. We now report the use of the diphenylphosphinoyl group in this role as a new approach to organic synthesis (Scheme 1).

The first carbon–carbon bond is made from an aldehyde and the anion of an alkyl diphenylphosphine oxide. Providing a lithium base (e.g. BuLi) is used to form the anion, only the first stage of the Horner-Wittig reaction occurs[2] and an alcohol (**1**) is formed in high yield. Derivatives of these alcohols (**1**) (*e.g.* the tosylates) solvolyse in carboxylic acids (acetic, formic, or trifluoroacetic) at 25—75° with migration of the diphenylphosphinoyl group to give substituted allyl diphenylphosphine oxides (**2**) as the only products.[3] No alkyl migration is ever observed. Treatment of (**2**) with butyl lithium removes the proton from what was the aldehyde carbon atom, an example of umpolung,[4] giving an allyl anion which reacts with another aldehyde at the α-position with further extension of the carbon chain (**3**).

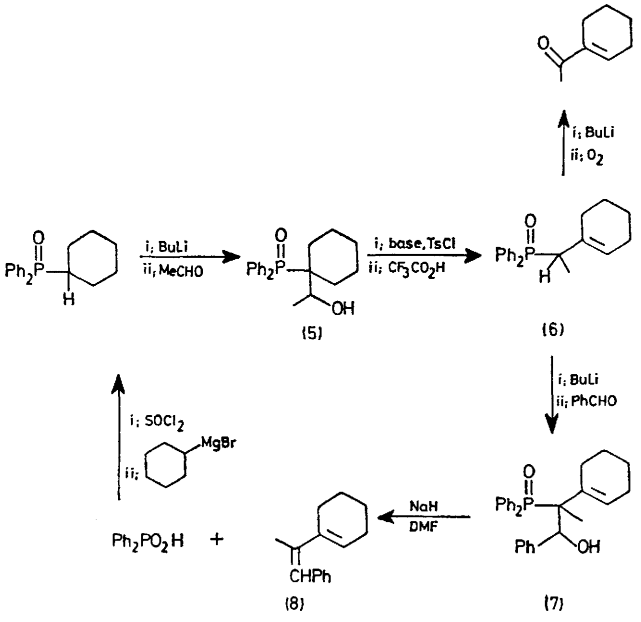
This sequence of carbon-carbon bond forming reactions followed by migration of the activating group could in principle be extended indefinitely. It may be terminated by removing the activating group in two ways. The Wittig reaction between phosphorus-stabilised ylides and oxygen is known to give carbonyl compounds,[5] though further reaction often occurs.[6] We have found that



Scheme 1

secondary alkyl diphenylphosphine oxides (*e.g.* **6**) react with butyl lithium and oxygen (air) to give ketones in moderate yields (*ca.* 50%). Alternatively, the normal conclusion of the Horner-Wittig reaction may be initiated by treating any of the 2-hydroxyalkyl diphenylphosphine oxides with sodium hydride.[7] The phosphorus-containing product from both these reactions is diphenylphosphinic acid which is far more easily separated from the organic product than the more conventional triphenylphosphine oxide. It can also be recycled. Reaction with thionyl chloride gives the acid chloride which reacts with Grignard reagents to give alkyldiphenylphosphine oxides (*e.g.* **4**) in high yield.[8]

Thus, the allyldiphenylphosphine oxide (**6**), formed by rearrangement of the alcohol (**5**), gives one of the alcohols (**7**) with considerable stereoselectivity and this alcohol gives a single diene (**8**) stereospecifically on treatment with sodium hydride.



Scheme 2

The complete sequence (Scheme 2), in effect combines an alkyl halide with a series of carbonyl compounds. The one activating group, Ph$_2$P(O), is used to link together a series of electrophilic molecules into a continuous carbon framework. Experiments in progress suggest this approach is generally applicable to a wide variety of structures. It provides extra versatility in synthetic design, particularly suited to the synthesis of crowded molecules.

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