Note

Desymmetrisation of a diallyl system by intramolecular Heck reaction

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Abstract

The development of a desymmetrising cyclisation of a benzylic diallyl iodide is reported. The final procedure generates a new quaternary chiral centre in greater than 80% yield giving a highly functionalised methylene indan product suitable for further application in synthesis.
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1. Introduction

The Heck reaction has established its place as a vital tool in organic synthesis, allowing the formation of carbon–carbon bonds under mild catalytic conditions, and the asymmetric intramolecular Heck has been applied to a wide range of syntheses [1]. Although widely applied, there are severe limitations to the asymmetric Heck reaction in terms of substrates, which is a reflection of the mechanism [2], which involves addition of an organopalladium halide to an alkene, followed by β elimination of palladium hydride to reform an alkene (Scheme 1).
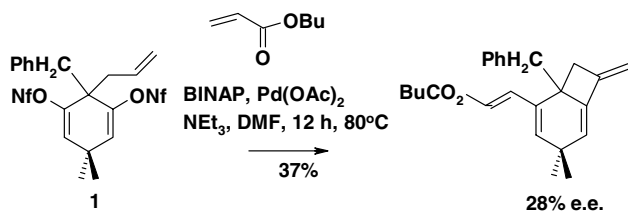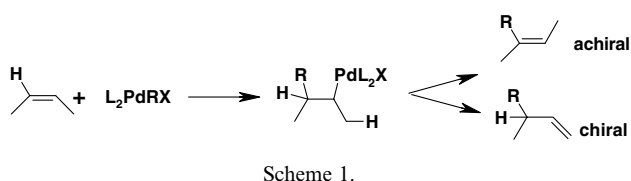
The original (achiral) Heck reaction involves the formation of a new bond to an alkene, by β hydride elimination towards the newly formed carbon–carbon bond, and asymmetric variations have been developed around strategies which involve the elimination of palladium hydride away from the newly formed carbon–carbon bond, giving the product of a double bond isomerisation with respect to the starting materials.

Such approaches have been successful, but are usually limited, at least in the case of generating tertiary chiral centres, to the use of cyclic alkenes [1] as these show good regioselectivity of double bond formation (i.e., selectivity for the chiral product) which is otherwise often difficult to control. Recently it has been shown that there is good selectivity in the asymmetric Heck reaction to give silane terminated alkenes, presumably reflecting the lability of the α-silyl hydrogen towards elimination [3].

One class of reaction which generates new chiral centres, regardless of the hybridisation of the reactive centres is the desymmetrisation [4], in which one of two enantiotopic groups (that is related by a mirror plane) is selectively attacked leaving the other unchanged, breaching the symmetry of the starting material and generating a new chiral centre. This strategy is particularly useful in the synthesis of precisely those types of products which are difficult with the Heck reaction, as the desymmetrisation reaction is not sensitive to substitution at the point of bifurcation, and thus is ideal for generating highly substituted chiral centres. Desymmetrisation is a popular tactic in organic synthesis, but has received surprisingly little attention in organometallic catalysis (although a range of metal-based oxidations and reductions are popular) with allylic substitution dominating the organometallic examples [4]. Surprisingly, only one report [5] was available in the literature of a desymmetrising Heck reaction, and this example is on a complex substrate **1**. In this case two enantio-

Scheme 1.

Scheme 2.

Table 1
Conditions and yield for desymmetrisation of 2

Entry	Solvent	Base	Catalyst	Temp.	Time	Yield
1	MeCN	NEt$_3$	PdCl$_2$(PPh$_3$)$_2$	RT	5 h	–
2	MeCN	NEt$_3$	PdCl$_2$(PPh$_3$)$_2$	80°	5 h	–
3	MeCN	NEt$_3$	Pd$_2$(dba)$_3$	RT	1 h	–
4	MeCN	NEt$_3$	Pd$_2$(dba)$_3$	80°	5 h	–
5	MeCN	HNEt$_2$	PdCl$_2$(PPh$_3$)$_2$	RT	5 h	Trace[a]
6	MeCN	HNEt$_2$	PdCl$_2$(PPh$_3$)$_2$	80°	1 h	10%[a]
7	DMF	HNEt$_2$	PdCl$_2$(PPh$_3$)$_2$	RT	1 h	77%[b]
8	DMF	HNEt$_2$	PdCl$_2$(PPh$_3$)$_2$	RT	5 h	86%[a]

[a] Estimated yield from crude NMR.
[b] Isolated yields.

topic nonflates are differentiated by dual inter and intra-molecular Heck reactions (Scheme 2).

It seemed that a simpler approach to the application of Heck reactions to desymmetrisation, which would give potentially more useful products, would be the intramolecular reaction of an aryl iodide with a bifurcated bisalkene chain To test the viability of the Heck reaction in desymmetrisation a prochiral diallyl benzyl alcohol **2** was synthesised in 55% yield by treatment of 2-iodomethyl benzoate with an excess of allyl magnesium chloride (Scheme 3), along with a by-product of double bond isomerisation **3** in 16% yield.

With the substrate **2** available a series of reaction conditions for the desymmetrising Heck cyclisation to the methylene indan **4** (Scheme 4) were screened using a variety of solvents, bases and palladium sources, summarised in Table 1. Omission of the additional phosphine leads to lowered yields in all cases.

The initial attempts followed a literature precedent [6] showing high efficient cyclisation to form a five-membered ring with palladium (II) salts in acetonitrile, but
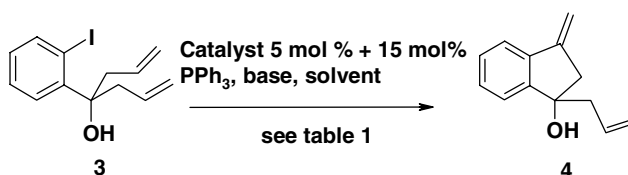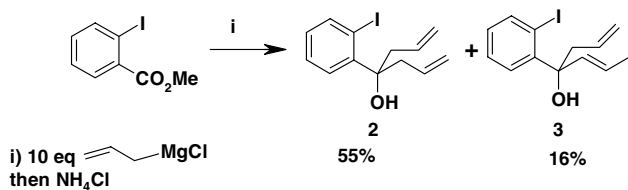
under these conditions no product was observed. Variations of base, palladium source and temperature proved ineffective in acetonitrile solvent, with some product being observed with the less hindered base diethylamine replacing triethylamine, and the use of PdCl$_2$(PPh$_3$)$_2$ rather than Pd$_2$(dba)$_3$, but a satisfactory yield was never obtained. Upon moving to the less polar solvent DMF, efficient cyclisation was observed with this base/palladium source combination even at room temperature, and by extending the reaction time an optimum combination was found to be DMF solvent with diethylamine as base, with palladium dichloride bis(triphenylphosphine) as the catalyst source with a reaction time of 5 h. Under these conditions the Heck reaction proceeded to give an 86% yield of 1-allyl-3-methylene-indan-1-ol **4** with no significant by-products. Although DMF is the more common solvent for the Heck reaction it is surprising that such a difference is noted between the solvents, especially given the precedent [6] for the efficiency of acetonitrile in cyclisation to a five-membered ring in another system. In the cases (entries 1–4) where no yield is given for product the starting material is recovered essentially unchanged, and thus it appears to be the initial oxidative insertion into the aryl iodide which is retarded in these cases rather than the cyclisation itself, hence it is difficult to see why variations in the reactivity of substrate alkenes could cause the apparent differences. The difference in polarity between acetonitrile ($\mu = 3.92$, $\varepsilon = 38$) and DMF ($\mu = 3.82$, $\varepsilon = 37$) is not great enough to explain the difference in reactivity, so other, substrate specific, factors may be important. The diallyl system could, potentially, coordinate to, and deactivate, palladium species and it may be that the palladium acetonitrile complexes likely to exist in such a solution are more easily deactivated by the diallyl system than the palladium species which exist in DMF solution, however it is more likely that the excess phosphine would coordinate to these species, and thus solvent effects are difficult to explain on these grounds. However, it has also been observed [7] that palladium nanoparticles can be important in Heck reactions and the stability of these may also be solvent dependant,

i) 10 eq ⟶ MgCl
then NH$_4$Cl

Scheme 3.

Catalyst 5 mol % + 15 mol% PPh$_3$, base, solvent

see table 1

Scheme 4.

although again why these effects should be important for this substrate and not others is far from clear.

Nevertheless, it has been shown that desymmetrising Heck reaction of a simple, easily accessible diallyl system proceeds smoothly to generate a new quaternary chiral centre in high yield, giving a highly substituted product containing two alkenes of different reactivities (one styrenoid, the other an isolated terminal alkene) which could be useful as a starting material in synthesis [8]. The range of diallyl and divinyl species which could similarly be simply prepared and desymmetrised is vast and we are currently investigating the cyclisation of similar diallyl systems, and asymmetric variations of this reaction using chiral ligand systems.

2. Experimental procedures

2.1. 4-(2-Iodophenyl)hepta-1,6-dien-4-ol, 2

To a solution of 2-iodomethylbenzoate (2.5 g, 9.5 mmol) in THF (25 ml) at 0 °C under an N_2 atmosphere was added drop-wise allyl magnesium chloride (10 M in ether, 12 ml, 120 mmol) over 10 min. The reaction mixture was allowed to warm to ambient temperature before being treated with saturated aqueous ammonium chloride, extracted in to DCM, dried (MgSO$_4$) and evaporated to dryness. Column chromatography gave **2** (Rf = 0.3, petrol:EtOc 95:5) as a colourless oil, 1.55 g, 55%, v_{max} 3548 3074 2989 1632 1574 δ H (400 MHz, CDCl$_3$) 7.91 (1H dd 7.7, 1.1 Hz, ArH6) 7.65 (1H, dd, 7.7, 1.5 Hz, ArH3) 7.32 (1H, app dt, 7.7, 1.1 Hz ArH4) 6.8 (1H app dt, 7.7, 1.5 Hz ArH5) 5.5 (2H, m, $2 \times H_2C=CH$) 5.1 (2H, dd, 10.4, 2.1 Hz, $2 \times C=CH_{cis}$) 4.9 (2H, dd, 15.5, 2.1, $2 \times C=CH_{trans}$) 3.3 (2H, dd, 14.2, 6.3 Hz, $2 \times 1/2$ CH_2) 2.55 (2H, dd, 14.2, 8.3 Hz, $2 \times 1/2$ CH_2); m/z (APCI)(%) 298 (M − H$_2$O + H$^+$)(11) 170 (28).

2.2. 1-Allyl-3-methyleneindan-1-ol, 4

To a Schlenk flask containing **2** (500 mg, 1.5 mmol) and PPh$_3$ (80 mg, 0.3 mmol) which had been repeatedly

evacuated and flushed with nitrogen was added dry and degassed DMF (5 ml) then PdCl$_2$(PPh$_3$)$_2$ (50 mg, 0.095 mmol) and Et$_2$NH (0.5 ml, 353 mg, 4.8 mmol). The mixture was sealed under an inert atmosphere and stirred for 5 h before being poured into a separating funnel, extracted into DCM, (10 ml) washed with sodium bicarbonate (saturated aqueous, 2×10 ml) water (2×50 ml) dried (MgSO$_4$) and evaporated to dryness. Column chromatography gave **4** as a colourless oil (Rf = 0.25, petrol:ethyl acetate 5:95) (256 mg, 86%) v_{max} 3384 3072 1641 1436; δH (400 MHz, CDCl$_3$) 7.45 (1H, dd, 7.0, 1.5 Hz ArH3) 7.30–7.22 (3H, m, $3 \times$ ArH) 5.75 (1H, m, C=CH) 5.39 (1H, t, 2.2 Hz, $1/2 \times$ indanC=CH_2) 5.15 (m, 2H, allylC=CH_2) 4.93 (1H, t, 2.2 Hz, $1/2 \times$ indanC=CH_2) 2.95 (1H, dt, 16.3, 2.2 Hz, $1/2 \times$ indanCH_2) 2.73 (1H, dt, 16.3, 2.2 Hz, $1/2 \times$ indanCH_2) 2.55 (1H, dd, 13.7, 6.9 Hz, $1/2 \times$ allyl CH_2) 2.45 (1H, dd, 13.7, 7.9 Hz, $1/2 \times$ allylCH_2); m/z (APCI)(%) 169 (M − H$_2$O+H$^+$)- (100).

Note added in proof

Very recently a paper was published relating to the desymmetrising Heck. Oestreich, M. Sempere-Culler, F. and Machotta, A.B., Angew. Chem. Int. Ed. Eng., 2005, 44, 149.

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