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Highly regio- and chemoselective palladium(0)-mediated allylic substitution of difunctional allylic halides with phenols

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ABSTRACT

An efficient Pd(0)-mediated, base-assisted reaction of phenols with difunctionalised allylic halides results in the formation of coupled products in good yields. The reactions proceed with excellent stereo-, regio- and chemocontrol. An appropriately functionalised Weinreb amide, synthesised by this methodology, undergoes halogen-lithium exchange and subsequent intramolecular 1,2-carbonyl addition/elimination to give an advanced macrocyclic intermediate with potential use in the synthesis of likonide B.

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Difunctional allylic sesquiterpenes and monoterpenes (Scheme 1, **1** and **2**, respectively) are useful synthetic building blocks, which have been successfully incorporated into various biologically active and medicinally relevant farnesyl[1,2] and geranylgeranyl derivatives.[3] Several synthetic methods have been described in the literature for accessing these types of difunctionalised allylic systems.[4,5] We envisaged that a difunctionalised terpene containing different allylic leaving groups (e.g., halide and acetate) would be amenable to Pd(0)-mediated allylic substitution processes.[6] This transformation requires the chemodifferentiation of two unique allyl leaving groups by Pd(0) (exemplified by leaving groups X and Y in generic compound **2** in Scheme 1). Such chemodifferentiation would depend on: (i) the relative ease of oxidative addition (rate of C–X bond cleavage) for the reaction of Pd(0) with **2** to give either **3** or **3′**; (ii) the stability of the oxidative addition products, strength of 'Pd(II)–X' versus 'Pd(II)–Y' bonds; (iii) any reversible oxidative addition reaction.

Pd(0)-catalysed allylic substitution leads to highly stereoselective substitution reactions and is unique for several reasons.[6b] It is often possible to attain both high stereoselectivity and regioselectivity, but chemoselectivity in reactions containing two types of allylic leaving groups in an acyclic system has not been well investigated.[7] Herein, we report a novel Pd(0)-catalysed allylic substitution of difunctionalised terpenyl halides, which proceeds in a highly stereo-, regio- and chemoselective manner. Suitable difunctionalised geranyl systems were identified as benchmark substrates for the evaluation of Pd(0)-catalysed allylic substitution reactions. For example, 8-hydroxygeranyl acetate **4** could be converted into halo-substituted geranyl acetates **5a** and **5b** (Scheme 2), using conventional procedures,[8] in good yields with high stereoselectivity (especially in the case of chloride; note that the iodide compound **5a** is light sensitive!). The presence of distinct functional groups allows the chemodifferentiation in the Pd(0)-catalysed allylic substitution to be tested.

Initial experiments were performed with both **5a** and **5b** and 4-methoxyphenol **6** (as the nucleophile) with NaH (base) under Pd(0)-catalysed conditions. It was found that only halide displacement was observed with allyl iodide **5a** giving higher regioselectivity (α-**7** was the only observed regioisomer) as compared to allyl chloride **5b** (where a ratio of 2.5:1, α-**7**/γ-**7**, was obtained). At the outset of our studies using **5a**, various phosphine ligands were screened in combination with [Pd^0_2(dba-3,5,3′,5′-OMe)$_3$] as the Pd(0) source.[9–11] The Pd(0) catalyst systems derived from simple phosphine ligands **8a–d** displayed higher reactivity (Table 1, entries 1–4).[12] Complete stereo- and regiocontrol was made possible by using such simple ligand systems, with **8c** identified as the most effective. Unfortunately, bulky electron-rich ligands **8e–g** (Table 1, entries 5–7) and electron-deficient ligand **8h** (entry 8) gave poor results also bringing about a reduction in the stereoselectivity. The allylic substitution reaction with phenols and base in the absence of Pd(0) proceeds with poor regio- and stereocontrol (lower yields were obtained too), highlighting the importance of the developed protocol with catalytic Pd(0) (entry 9).

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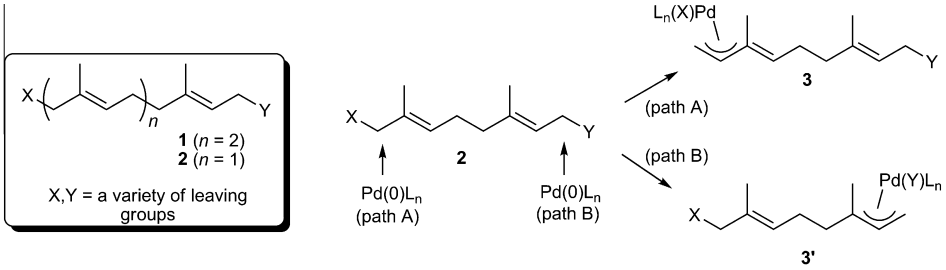
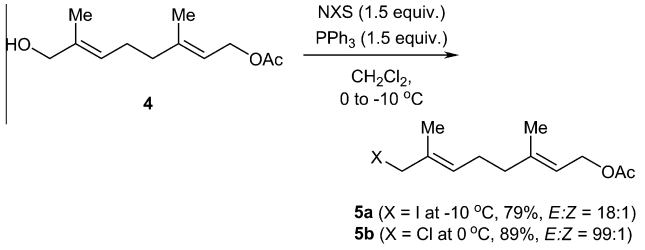
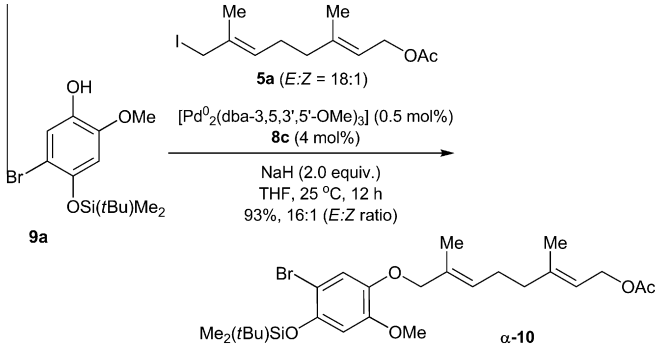


Scheme 1. Difunctionalised allylic derivatives, and proposed chemodifferentiation of allylic halide and acetate leaving groups by Pd(0).



Scheme 2. Synthesis of bifunctional geranyl acetates **5a** and **5b**.

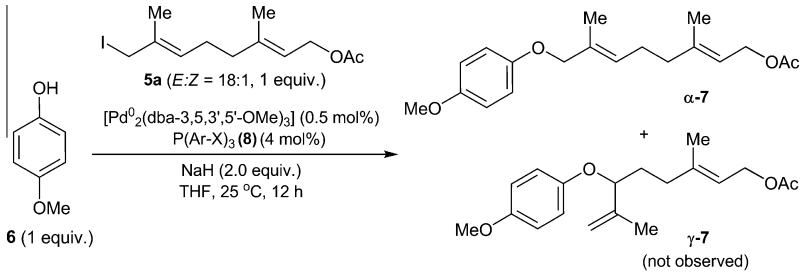


Scheme 3. Evaluation of a highly substituted phenol coupling partner **9a**.

With an effective catalytic system in hand, using **8c** as the ligand of choice, we explored its scope in the coupling of a more sterically hindered phenol **9a** with **5a** to give α-**10** in 93% yield and 16:1 stereoselectivity (Scheme 3). Phenol **9a** contains a labile silyl protecting group, which was tolerated in this reaction highlighting the mildness of the synthetic protocol.

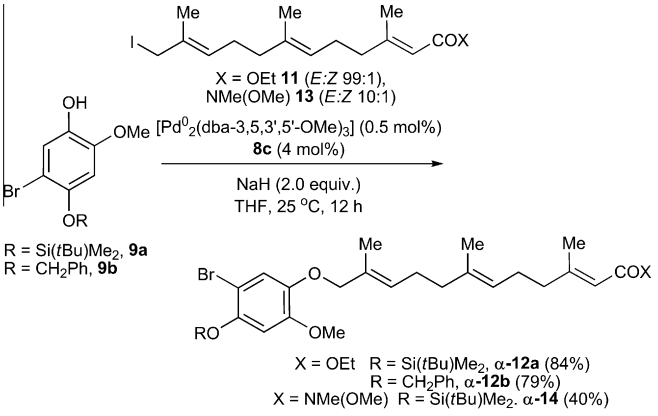
Farnesyl pyrophosphates (FPP) are important intermediates used by organisms for the biosynthesis of various classes of natural products.[13] Likonides A and B are one such class, which possess an embedded 'farnesyl' motif (vide infra).[14–16] Indeed, we recognised that the Pd(0)-mediated allylic substitution protocol could be used in the synthesis of potentially useful intermediates to these compounds. Accordingly, a functionalised farnesyl iodide **11** was coupled with both substituted phenols **9a** and **9b** using the Pd(0)-mediated allylic substitution protocol (Scheme 4). In line with the earlier results, using **8c** as the ligand, complete regio- and stereocontrol (from allylic starting material **11** to product, either α-**12a** or α-**12b**) was observed. In these reactions, neither the vinyl ester nor the aromatic bromides caused any problems in terms of the catalysis. Synthetically more relevant functional groups could also be incorporated via this methodology. Accordingly, a farnesyl iodide containing a Weinreb amide functionality **13** was reacted with substituted phenol **9a** giving the coupled product α-**14** with complete regio- and stereocontrol (Scheme 4).

Table 1
Pd(0)-catalysed allylic alkylation catalyst screening

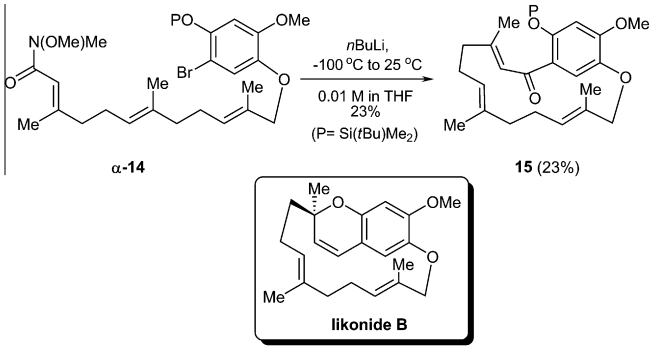


Entry	Ligand {P(Ar-X)3}		E:Z ratio[a]	Yield α-**7**[b] (%)
1	PPh_3	**8a**	18:1	79
2	$P(4\text{-}FC_6H_4)_3$	**8b**	18:1	89
3[c]	$P(4\text{-}MeOC_6H4)_3$	**8c**	18:1	94
4	$P(4\text{-}MeC_6H_4)_3$	**8d**	15:1	81
5	$P(2,4,6\text{-}Me_3C_6H_2)_3$	**8e**	15:1	54
6	PCy_3	**8f**	15:1	68
7	$t\text{-}Bu_3P{\cdot}HBF_4$	**8g**	12:1	32
8	$P(OPh)_3$	**8h**	15:1	84
9[d]	—	—	3:1	59

[a] *E:Z* ratio calculated from the ^1H NMR spectra of the crude products (>99% α-**7b**; γ-**7b** not observed).
[b] Isolated yield following purification by flash chromatography on silica gel with the product showing complete chemoselectivity for iodide over acetate.
[c] Under otherwise identical conditions, using $Pd_2(dba\text{-}H)_3$, a 76% yield was recorded.
[d] Absence of palladium precursor and ligand (1:1 ratio of α-**7b**/γ-**7b**).



Scheme 4. Synthesis of farnesyl-substituted compounds.



Scheme 5. Macrocyclic ketone **15** formation from Weinreb amide α-**14**.

To the best of our knowledge Weinreb amides have not been used to form macrocyclic ketones. We postulated that the aromatic bromide component of α-**14** could undergo halogen-lithium exchange at low temperature and high dilution, followed by an intramolecular 1,2-carbonyl addition/elimination sequence with the suitably disposed vinyl amide motif (Scheme 5). Rather pleasingly, the in situ generated aromatic lithium derivative of α-**14** was found to undergo macrocyclisation (at −100 to 25 °C) to afford **15** in 23% yield. In this case, only the 16-membered macrocyclic product was isolated from the reaction mixture (by flash chromatography on silica gel).

In summary, a convenient protocol for the synthesis of geranyl and farnesyl derivatives by Pd(0)-mediated allylic substitution, which proceeds with excellent regio-, stereo- and chemocontrol, has been developed. In preliminary studies, a macrocyclic ketone **15**, which is, potentially, an advanced intermediate for the synthesis of likonide B[15,16] could be synthesised using a novel macrocyclisation strategy from α-**14**.

Acknowledgements

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12. *Representative procedure for allylic substitution*: A solution of $[Pd^0_2(dba\text{-}3,5,3',5'\text{-}OMe)_3]$[9] (0.0031 mmol, 0.5 mol %) and phosphine (0.024 mmol, 4 mol%) in THF (2 mL) at 25 °C was stirred for 10 min under N_2. To this was added 8-iodo-3,7-dimethyl-(2*E*,6*E*)-octadien-1-yl acetate (**5a**) (0.20 g, 0.62 mmol) and the reaction mixture was allowed to stir for 5 min. In a separate operation, a solution of phenol (**6**) (0.62 mmol) in THF (2 mL) was added to NaH (60% emulsion in oil) (2 equiv, 1.24 mmol) at 0 °C under N_2. The resulting solution was added to the reaction mixture and stirred at 25 °C for the desired time. On completion, the reaction was quenched with H_2O (5 mL) and then extracted with Et_2O (10 mL). The organic layer was separated, dried over $MgSO_4$ and filtered. Concentration in vacuo gave the desired products as oils. All compounds were separated by flash chromatography on silica gel using hexane/EtOAc mixtures as the eluent. Representative data for (2*E*,6*E*)-8-(4-methoxyphenoxy)-3,7-dimethyl-2,6-octadienyl acetate (α-**7**). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 1.69 (s, 3H), 1.71 (s, 3H), 2.04 (s, 3H), 2.08–2.25 (m, 4H), 3.75 (s, 3H), 4.31 (s, 2H), 4.58 (d, 2H, *J* = 7.1 Hz), 5.35–5.38 (m, 1H), 5.48–5.51 (m, 1H), 6.75–6.91 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 16.3, 18.8, 23.4, 28.2, 41.3, 58.0, 63.8, 78.5, 114.2, 116.9, 118.2, 123.5, 134.0, 144.2, 152.4, 156.1, 173.7; LRMS (CI) *m/z* (rel.%): 336 (M^++NH_4^+, 20%), 318 (M^+, 30), 275 (50), 259 (60), 135 (100); HRMS (CI) *m/z* exact mass calculated for $C_{19}H_{26}O_4$+NH_4^+ 336.2188; found 336.2177. Selected data for regioisomer, γ-**7**: ^{1}H NMR (400 MHz, $CDCl_3$) 1.69 (s, 3H), 1.73 (s, 3H), 2.04 (s, 3H), 2.08–2.12 (m, 2H), 2.14–2.19 (m, 2H), 3.75 (s, 3H), 4.59 (d, 2H, *J* = 6.6 Hz), 4.61 (t, 1H, *J* = 6.7 Hz), 5.01 (d, 1H, *J* = 1.3 Hz), 5.02 (d, 1H, *J* = 1.3 Hz), 5.28–5.31 (m, 1H), 6.72–6.89 (m, 4H).
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