Palladium-catalyzed allylic substitution on solid support

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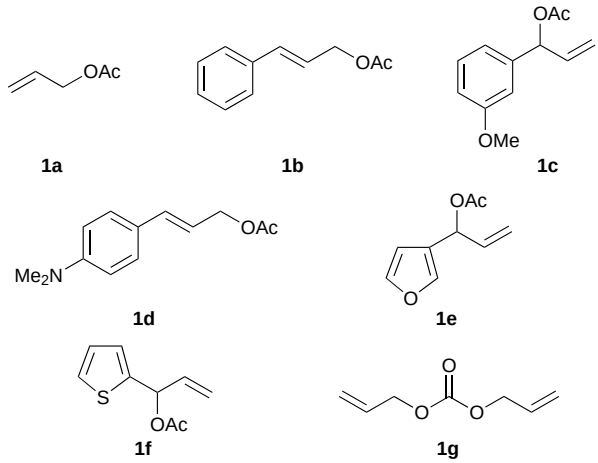
Different polymer-bound 1,3-dicarbonyl compounds react as nucleophiles in Pd-catalyzed allylic substitutions on solid support with a variety of allylic acetates, chlorides and carbonates.

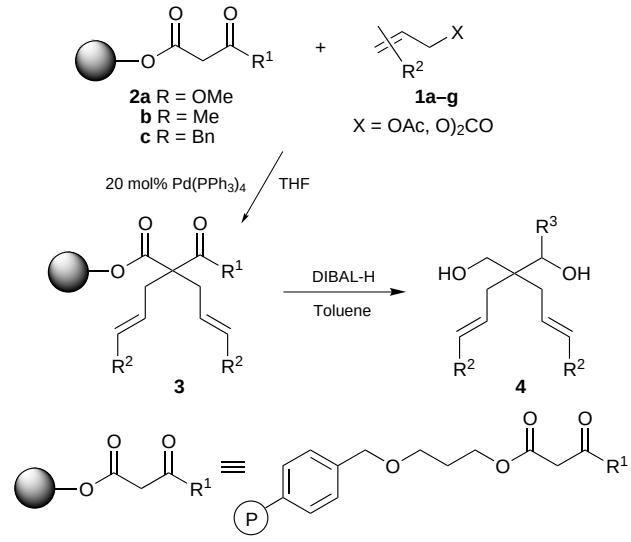
Combinatorial chemistry is regarded as a powerful tool to improve the search for new pharmacologically interesting compounds.[1] In most of the cases solid phase synthesis is used to generate combinatorial libraries, which are subsequently tested for their biological activity. Therefore, the development of basic carbon–carbon bound-forming reactions on the solid phase is an important task, especially in combinatorial synthesis of organic compounds of low molecular weight.

In the course of our studies on the use of resin-linked 1,3-dicarbonyl compounds to build up combinatorial libraries, we have previously reported on a two-component domino–Knoevenagel–ene reaction[2] and a three-component domino–Knoevenagel-hetero-Diels–Alder reaction[3] to afford structurally diverse cycloalkanes and 3,4-dihydro-2*H*-pyrans, respectively. Furthermore, we established an efficient method to synthesise highly diverse pyrazolones by treatment of a variety of polymer-bound β-keto esters with hydrazine derivatives, resulting in concomitant release of the final products from the support.[4]

Herein, we report on the use of polymer-bound 1,3-dicarbonyl compounds in Pd^0-catalyzed allylic substitution reactions with a variety of allylic substrates **1a**–**g**, **5** and **8a**,**b**. The Pd-catalyzed allylation[5] is well known for its high control of stereoselectivity and functional group tolerance, as well as good yields, and is therefore of great interest for combinatorial chemistry.[6]



Polymer-bound malonate **2a** and acetoacetates[2,3] **2b** and **2c** reacted with a variety of aliphatic and aromatic allylic acetates **1a**–**f** (5 equiv., Scheme 1) in the presence of 20 mol% of tetrakis(triphenylphosphine)palladium as a catalyst and bis-(trimethylsilyl)acetamide (BSA)[7] as a base (5 equiv.) in THF at reflux temperature for 6–15 h. The resin-bound products **3** were cleaved under reductive conditions with DIBAL-H (10 equiv., toluene, 0 °C, 12 h) to afford the desired diols **4a**–**h** in 20–57% overall yield based on the concentration of free hydroxy groups



Scheme 1

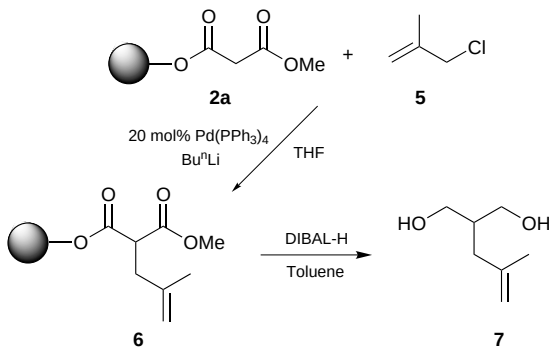
in the spacer-modified polystyrene-resin (0.75 mmol per gram resin)[2] (Table 1). Using the sterically less hindered allylic acetates **1a**–**f** dialkylation was observed in all cases, showing the expected high reactivity of the polymer-bound β-keto esters **2a**,**b** towards allylic substitution.

In addition to the allylic acetates, allylic chlorides and carbonates were also used. Employing allylic carbonates, no addition of base is required since the carbonate moiety reacts as a leaving group and simultaneously forms an alkoxide as a base after loss of carbon dioxide.[5] Thus, reaction of diallyl carbonate **1g** (3 equiv.) with the polymer-bound benzyl-substituted acetoacetate[4] **2c** was performed at room temperature in THF for 1 h using 10 mol% Pd catalyst. After cleavage from the resin the dialkylated product **4i** was obtained in 76% yield, showing the very high reactivity of allylic carbonates (Table 1). In the case of β-methallyl chloride **5**, Bu^nLi (1 equiv.) was used as base and the reaction was performed at room temperature for 21 h. In this

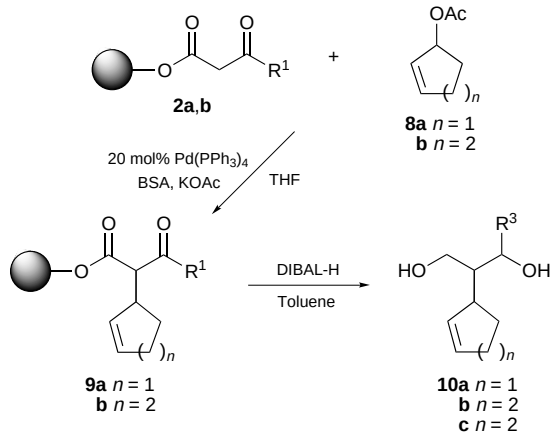
Table 1 Synthesised 1,3-diols **4**

Substrates		Products				
1	**2**	**4**	R^1	R^2	R^3	Overall yield (%)[a]
a	**a**	**a**	OMe	H	H	30
b	**a**	**b**	OMe	Ph	H	57
b	**b**	**c**	Me	Ph	Me	40
c	**b**	**d**	Me	3-$MeOC_6H_4$	Me	23
d	**b**	**e**	OMe	4-$Me_2NC_6H_4$	Me	34
e	**a**	**f**	OMe	3-Furyl	H	20
e	**b**	**g**	Me	3-Furyl	Me	23
f	**b**	**h**	Me	2-Thienyl	Me	20
g	**c**	**i**	Bn	H	Bn	76[b]

[a] The products were purified by flash chromatography. The yields are based on the concentration of free hydroxy groups in the spacer-modified polystyrene-resin (0.75 mmol per gram resin) (ref. 2). [b] No base was used. The reaction was performed at room temperature.



Scheme 2



Scheme 3

reaction only monoalkylation was observed. Thus, after reductive cleavage product **7** was obtained in 28% yield (Scheme 2).

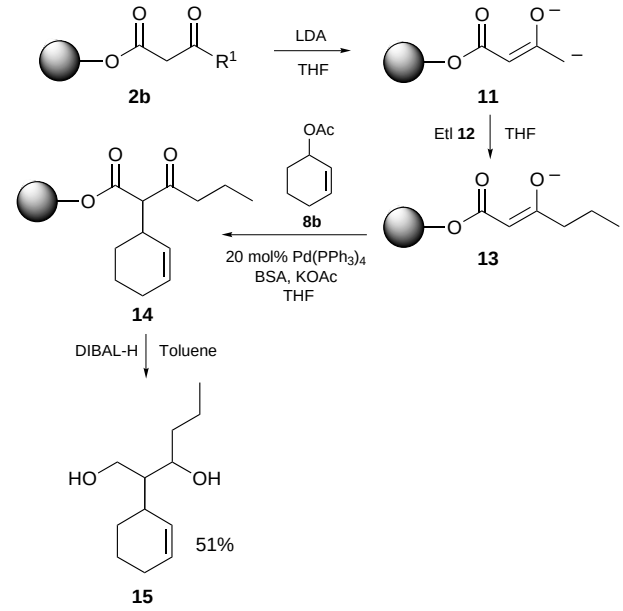
Selective monoalkylation could also be achieved using sterically more hindered cyclic allylic acetates (Scheme 3). Under the conditions described for **1a**–**f** [20 mol% $Pd(PPh_3)_4$, BSA, KOAc, THF, reflux, 10 h] the reaction of the cyclic acetates **8a**,**b** and **2a**,**b** gave after reductive cleavage the desired diols **10a**–**c**, respectively, in 40–59% yield (Table 2). The formation of the dialkylated products was not observed.

Table 2 Synthesis of the 1,3-diols **10**

Substrates		Products				
2	**8**	**10**	*n*	R^1	R^3	Overall yield (%)[a]
a	**a**	**a**	1	OMe	H	53
a	**b**	**b**	2	OMe	H	40
b	**b**	**c**	2	Me	Me	59

[a] The products were purified by flash chromatography. The yields are based on the concentration of free hydroxy groups in the spacer-modified polystyrene-resin (0.75 mmol per gram) (ref. 2).

A further possibility to increase diversity in a one-pot procedure is shown in Scheme 4. As previously described by our group,[4] γ-alkylation of polymer-bound acetoacetate **2b** can be achieved by generating the dianion **11** with LDA at 0 °C and subsequent treatment with an alkylating reagent in THF at 0 °C, *e.g.* iodoethane **12**. The resulting monoanion **13** can now react as a nucleophile in an allylic substitution with **8b** to give the



Scheme 4

resin-bound product **14**, which was reductively cleaved as described above to afford the diol **15** in 51% overall yield.

In conclusion, we have shown that the Pd-catalyzed allylic substitution of allylic substrates such as acetates, chlorides and carbonates with different polymer-bound 1,3-dicarbonyl compounds is a very efficient C–C bond-forming reaction. Since allylic substrates are readily available building blocks, the solid phase reaction presented above should be amenable for combinatorial synthesis. Furthermore, the development of a one-pot protocol consisting of γ-alkylation and α-allylation of solid supported acetoacetate provides an even greater diversity of the desired products. We are currently investigating the possibility of using vinylic epoxides and bisallylic templates as substrates and resin-bound allylated 1,3-dicarbonyl compounds for further transformations.

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Notes and References

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