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Solid-Phase C–C and C–O Bond Forming Reactions Using 'Traceless' π-Arene–Chromium Linkers

James H. Rigby* and Mikhail A. Kondratenko

Department of Chemistry, Wayne State University, Detroit, MI 48202-3929, USA

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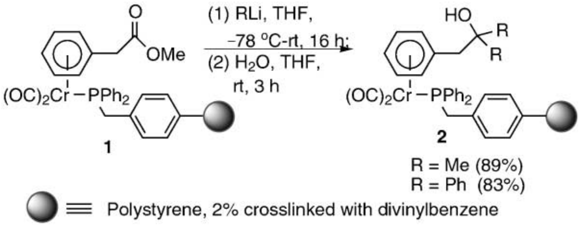
Abstract—The scope of solid-phase reactions utilizing a 'traceless' π-arene–chromium linker has been expanded to include the addition of organo-lithium reagents to a supported ester group, generation and alkylation of an enolate anion, and substitution via the Mitsunobu reaction. Immobilization of *ortho*-disubstituted polyfunctionalized arene chromium dicarbonyl species onto the solid support and subsequent, selective transformation is also reported. © 2002 Elsevier Science Ltd. All rights reserved.

Polymer-supported reagents provide an attractive and practical method for the preparation of novel chemical libraries with potential applications in the pharmaceutical industry. To date, solid-phase synthesis techniques have been successfully employed in the preparation of a wide variety of compounds including natural products.[1] Synthesis of complex molecular libraries requires judicious choice of linker properties as well as a viable synthetic pathway. Therefore, the development of new linkers and adoption of well-established solution-phase methodologies to the solid-phase format have attracted widespread attention over the last several years.[2]

As part of our program to develop new solid-phase synthetic methods, we became interested in exploring the use of polymer-supported π-arene–chromium carbonyl complexes. Recently, we reported an approach for the efficient loading of arene chromium carbonyl fragments onto a polystyrene resin.[3] This loading strategy has been successfully applied to the solid-phase synthesis of tertiary alcohols and esters. Results from our group as well as others[4] in the area of transition-metal linkers prompted us to expand the scope of chemical transformations that could be effected with polymer-anchored arene–chromium carbonyl compounds.

We first turned our attention to carbon–carbon bond forming reactions. Polystyrene-anchored ester **1** was chosen as a model substrate to work out the synthetic protocol. Treatment of **1** with alkyl- and aryl-lithium compounds followed by quenching with water afforded tertiary alcohols **2** in high yields (Scheme 1). Addition of two equivalents of organo-lithium reagents was observed exclusively. No intermediate ketones were detected in the crude product even when excess ester was used. This observation can be attributed to the slow diffusion of reagents into the resin.

Previous studies from our group had found that the solid support suppressed enolization of ketones and esters in the presence of Grignard reagents.[3] However, enolate-anions are among the most important intermediates in organic synthesis, serving crucial roles in a diverse array of modern synthetic methods. For that reason, it was important to find appropriate conditions for the enolization of polymer-incorporated species such as **1**. Formation of the enolate-anion **3** was readily achieved through reaction of **1** with lithium diisopropylamide (LDA)[5] (Scheme 2). Subsequent treatment of intermediate **3** with appropriate electrophiles furnished the corresponding α-substituted esters **4** in almost



Scheme 1.

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*Corresponding author. Tel.: +1-313-577-3472; fax: +1-313-577-3585; e-mail: jhr@chem.wayne.edu

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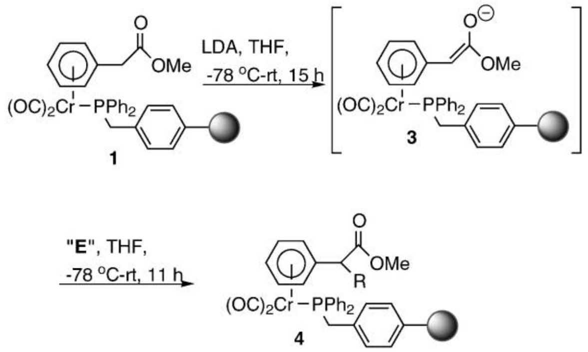
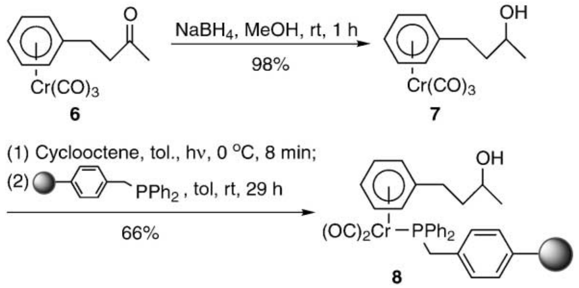
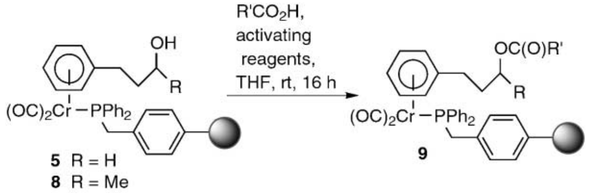


Scheme 2.



Scheme 3.



Scheme 4.

quantitative yields (Table 1). The high yields of desired products and the absence of side products observed in the reaction is a characteristic feature of solid-supported processes. Being attached to the polymeric scaffold, the bound species can only interact with reagents in the solvent media. In the current case, contact between ester and enolate functions was virtually precluded, thereby minimizing competition from Claisen condensation pathways and augmenting the alkylation reaction channel of **3**.

Table 1.

Entry	Electrophile (‘E’)	R	Yield (%)
1	D_2O	D	99
2	Benzyl bromide	$PhCH_2$	97
3	Allyl bromide	$CH_2{=}CHCH_2$	95

We were also interested in investigating the compatibility of a π-arene–chromium linker with the well-known Mitsunobu reaction conditions. The Mitsunobu reaction is a useful synthetic tool that allows for the conversion of an alcohol into a wide variety of functional groups. Reactivities of primary and secondary alcohols were tested in the present study. The solid-supported secondary alcohol **8** was prepared in three steps starting from non-supported ketone **6** (Scheme 3). The ketone **6** was reduced with sodium borohydride to give the corresponding alcohol **7** in excellent yield (98%), which was then converted into the polystyrene-supported derivative **8** using standard conditions.[3] It must be noted that the level of secondary alcohol fragment loading was found to be much lower than other substrates (66% vs 84–95%). To our surprise, formation of **8** was accompanied by partial decomposition and formation of polymer-bound $Cr(CO)_5$ species. The search for a more efficient pathway to secondary polymeric alcohols is currently in progress.

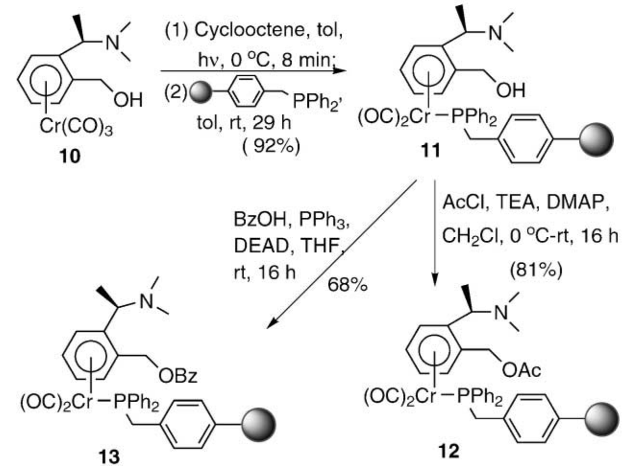
Alcohols **5** and **8** were found to be amenable to the Mitsunobu reaction. Mitsunobu esterification took place using diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) with triphenylphosphine[6] to produce the expected compounds **9** in good yields (Scheme 4, Table 2). An ethereal solvent such as THF was the media of choice for this transformation.

As shown in Table 2, employing either DEAD or DIAD as well as varying the substituents around the phenyl ring of the nucleophile did not appreciably influence the yield of **9**. Both primary and secondary alcohols exhibited the same reactivity under these conditions. Significantly, the presence of triphenylphosphine in the reaction mixture did not initiate cleavage of the arene–chromium bond as might be expected, and the resultant esters **9** were easily separated from the side products (i.e., the phosphine oxide and the hydrazinedicarboxylate esters) by filtration. The ability of the secondary alcohol **8** to undergo Mitsunobu reaction offers an attractive opportunity for the creation of a stereogenic center with control of absolute configuration.

All transformations of polystyrene-supported arene chromium complexes presented above and reported before[3,4,7] have been effected with benzene or monosubstituted arene derivatives. To expand the scope and

Table 2.

Starting alcohol	Activating reagents	Nucleophile	R	R′	Yield (%)
5	PPh_3, DEAD	Benzoic acid	H	C_6H_5	76
5	PPh_3, DEAD	4-Nitro-benzoic acid	H	p-$NO_2(C_6H_4)$	69
8	PPh_3, DEAD	Benzoic acid	CH_3	C_6H_5	78
8	PPh_3, DEAD	4-Nitro-benzoic acid	CH_3	p-$NO_2(C_6H_4)$	71
8	PPh_3, DIAD	Benzoic acid	CH_3	C_6H_5	79
8	PPh_3, DIAD	4-Nitro-benzoic acid	CH_3	p-$NO_2(C_6H_4)$	74



Scheme 5.

the diversity of the polymer-bound arene chromium substrates, it has now been demonstrated that polysubstituted, multifunctional arenes are also amenable to loading and subsequent chemical transformations on solid support. *ortho*-Disubstituted aminoalcohol **10**[8] served as a model compound for this investigation (Scheme 5). Using a standard two-step approach, one CO group in **10** was replaced with polystyrene diphenylphosphine to afford exclusively the resin-bound aminoalcohol **11** in 92% yield. This material was then selectively converted into the corresponding esters **12** and **13** by acylation with an AcCl/TEA/DMAP mixture or under Mitsunobu conditions, respectively.[9,10]

In conclusion, conditions for carbon–carbon bond forming reactions, via addition of organo-lithium reagents and alkylation via ester enolates, with solid-supported π-arene–chromium carbonyl complexes have been developed. The Mitsunobu reaction has been successfully applied to esterification of polymer-attached π-arene–chromium alcohols, and the capability for efficient loading and derivatizing polysubstituted, multifunctional arene–chromium carbonyls on solid support has also been demonstrated.

Acknowledgements

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9. In each of the above studies, the evaluation of the efficiency of substrate loading and the subsequent solid-phase transformations (Schemes 1–5) was determined by cleaving the organic substrates from the resin under acetonitrile-assisted[3] or photochemical conditions.[4b]
10. All new compounds exhibited spectral (^{1}H NMR, ^{13}C NMR, IR) and analytical (elemental analysis or HRMS) data fully consistent with the assigned structures.