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# A Facile and Highly Efficient Route to a Traceless $\pi$-Arene Chromium Linker. Applications to Synthetic and Combinatorial Chemistry

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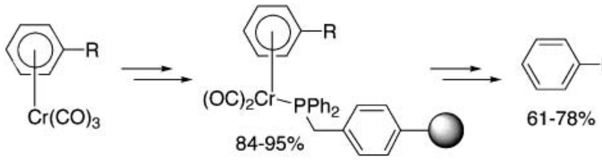
## ABSTRACT



**A simple and efficient method for the attachment of functionalized arene chromium carbonyls to a polymeric support has been developed. A highly efficient solid-phase synthesis of tertiary alcohols and esters was performed in a traceless manner using this strategy. The linker-fabrication protocol permits simultaneous immobilization of various substrates on the solid support.**

Over the past decade, polymer-supported reactions have been the subject of considerable study as a result of the increasing significance of combinatorial chemistry and multiple parallel synthesis.[1] The design of new linkers has been important to the success of this endeavor since linker diversity permits a broader scope of substrates and reagents to participate in solid-phase chemistry. Currently, many groups are focused on developing so-called “traceless” linkers, which are designed to leave a minimal vestige of the solid support upon release of the product.[2,3] In this context, the use of $\pi$-arene chromium complexes for loading the substrates onto a solid support offers attractive opportunities,[4] because the arene-chromium moiety is compatible with most functional groups. Recently, the Gibson and Maiorana laboratories have reported on the preparation of resin-bound $\pi$-arene chromium carbonyl complexes.[5] However, these approaches have, to date, afforded only modest yields of the polymer-attached complexes, and they are characterized by significant decomposition and side product formation. Herein we disclose a simple and efficient method for incorporating arene chromium carbonyls onto a polystyrene-based resin and demonstrate the utility of the resultant material in preparative and combinatorial chemistry.

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[1] Obrecht, D.; Villalgordo, J. M. In *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Baldwin, J. E., Williams, R. M., Eds.; Tetrahedron Organic Chemistry Series. Pergamon: Oxford, 1998.

[2] For recent reviews, see: (a) Comely, A. C.; Gibson, S. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1013. (b) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091. (c) Zaragoza, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2077. (d) Bräse, S.; Dahmen, S. *Chem. Eur. J.* **2000**, *6*, 1899.

[3] For some recent publications, see: (a) Tumelty, D.; Cao, K.; Holmes, P. *Org. Lett.* **2001**, *3*, 83. (b) Kirchhoff, J. H.; Brase, S.; Enders, D. *J. Comb. Chem.* **2001**, *3*, 71. (c) Horton, J. R.; Stamp, L. M.; Routledge, A. *Tetrahedron Lett.* **2000**, *41*, 9181. (d) Lormann, M.; Dahmen, S.; Brase, S. *Tetrahedron Lett.* **2000**, *41*, 3813. (e) Pourbaix, C.; Carreaux, F.; Carboni, B.; Deleuze, H. *Chem. Commun.* **2000**, 1275. (f) Schiemann, K.; Showalter, H. D. H. *J. Org. Chem.* **1999**, *64*, 4972. (g) Stieber, F.; Grether, U.; Waldmann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1073. (h) Comely, A. C.; Gibson, S. E.; Hales, N. J. *Chem. Commun.* **1999**, 2075.

[4] Semmelhack, M. F.; Hilt, G.; Colley, J. H. *Tetrahedron Lett.* **1998**, *39*, 7683.

[5] (a) Gibson, S. E.; Hales, N. J.; Peplow, M. A. *Tetrahedron Lett.* **1999**, *40*, 1417. (b) Maiorana, S.; Baldoli, C.; Licandro, E.; Casiraghi, L.; De Magistris, E.; Paio, A.; Provera, S.; Seneci, P. *Tetrahedron Lett.* **2000**, *41*, 7271.

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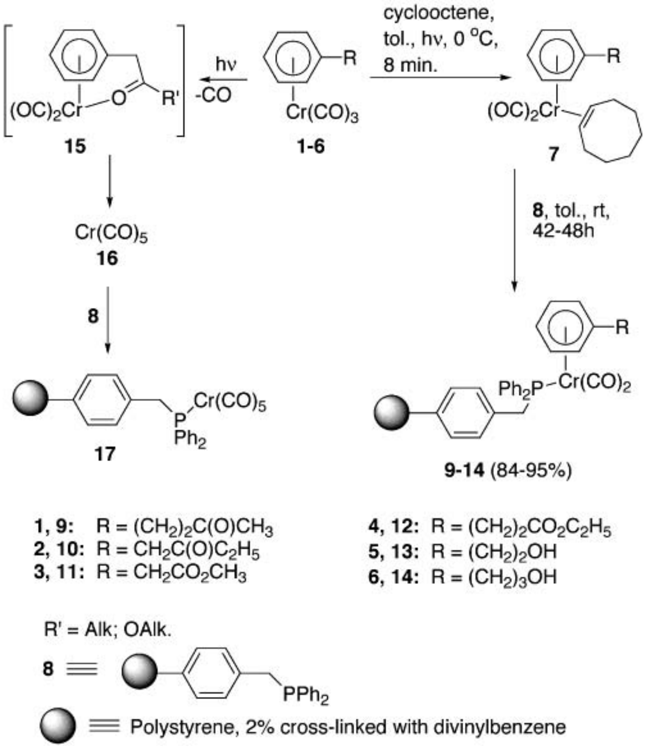
Polystyrene-supported arene chromium carbonyls **9**−**14** were prepared from complexes **1**−**6** via intermediate complex **7** using a two-step protocol,[5b,6,7] (Scheme 1).

**Scheme 1**

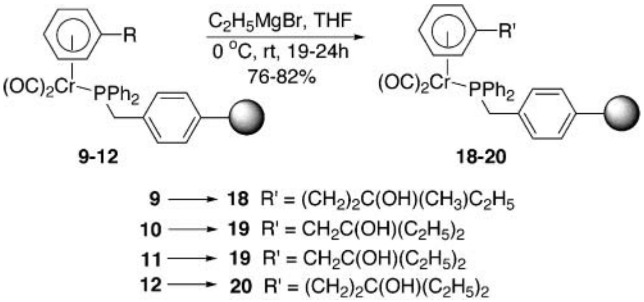


In contrast to the resin-bound benzene and toluene chromium carbonyls,[6] the synthesis of **9**−**14**, each of which exhibits an oxygen in the side chain, resulted in partial decomposition, thereby contaminating the final products with polymer-bound chromium pentacarbonyl phosphine **17** (Scheme 1). This problem was successfully overcome by using a large excess of cyclooctene (70−80 equiv). Under conditions found to be optimal (toluene, 0 °C, *hν*, 8 min), complexes **9**−**14** were obtained in high yields (84−95%), and no evidence of decomposition was noted. In the decomposition pathway it is likely that $Cr(CO)_5$ fragment **16**, derived from putative intermediate **15**, successfully competes with cyclooctene complex **7** to form the undesired phosphine **17**. Upon photolysis the chromium−oxygen bond in **15** is formed by attack of readily available heteroatom lone pair at the vacant coordination site on chromium. A large quantity of cyclooctene suppresses this chromium−oxygen bond formation, ensuring the preferred formation of the required intermediate **7**.

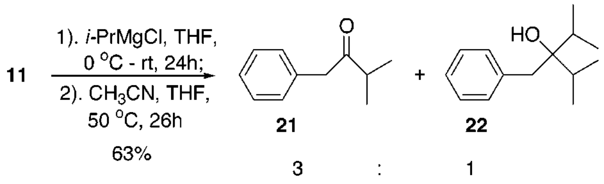
Products **9**−**14** were isolated as yellow beads, and their structures were assigned by IR spectroscopy.[8] The level of (arene)$Cr(CO)_2$ fragment loading was determined in two ways: (1) on the basis of isolated weighs of **9**−**14** (84−95%) and (2) on the basis of the amount of substrate released after subsequent cleavage of the arene-chromium bond (82−92%). Both methods showed similar results.

Ketones **9**, **10** and esters **11**, **12** were exposed to Grignard reagents in order to study the reactivity and synthetic utility of these polymer-bound species. It was found that ethylmagnesium bromide underwent addition to **9**−**12** to furnish the corresponding tertiary alcohols **18**−**20** in 76−82% yields (Scheme 2). The structures assigned to **18**−**20** were consistent with their IR spectra. Disappearance of the C=O stretches at 1736−1714 $cm^{-1}$ and the appearance of OH absorptions at 3571−3562 $cm^{-1}$ indicated that the C=O groups were converted into the desired alcohols. Reaction of **11** with *i*-PrMgCl followed by decomplexation afforded a mixture of 3-methyl-1-phenyl-2-butanone **21** and 2-isopropyl-3-methyl-1-phenyl-2-butanol **22** in a ratio of 3:1 and 63% overall yield (Scheme 3), suggesting that monoadditions to ester functions may be possible under certain circumstances. More importantly, no starting materials were detected in the crude products depicted in Schemes 2 and 3.

**Scheme 2**



**Scheme 3**



It is important to emphasize that the addition of the Grignard reagent to polymer-attached ketones **9** and **10** and esters **11** and **12** proceeded chemoselectively. No evidence

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(6) Rigby, J. H.; Kondratenko, M. A.; Fiedler, C. *Org. Lett.* **2000**, *2*, 3917.

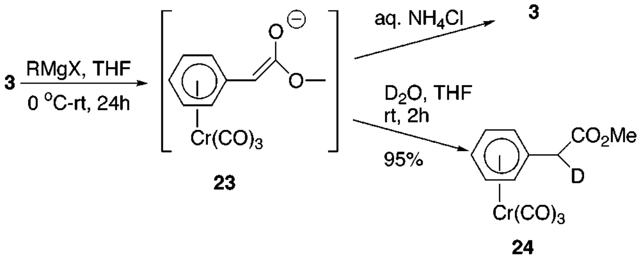
(7) Jaouen, G. *Tetrahedron Lett.* **1973**, 52, 5159.

(8) Compounds **9**−**14** exhibited two intense bands at 1885−1827 $cm^{-1}$ that corresponded to a $[Cr(CO)_2(PR3)]$ fragment. Additionally, ketones **9** and **10**, esters **11** and **12**, and alcohols **13** and **14** revealed the keto- (1716−1714 $cm^{-1}$), ester- (1736−1733 $cm^{-1}$), and hydroxy-group (3568 $cm^{-1}$) absorptions, respectively.

of competitive additions to the metal-bound CO groups was observed. Furthermore, addition of RMgX to the carbonyl groups was not accompanied by enolization.[9] The high chemoselectivity of **9**−**12** toward Grignard reagents may be attributed to steric hindrance created by the polymeric scaffold.

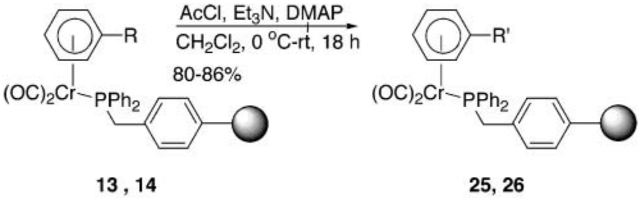
The crucial role of the solid support in the selective formation of **18**−**20** was supported by the fact that only starting material was recovered when unbound **3** was treated with EtMgBr or *i*-PrMgCl and subsequently quenched with aqueous $NH_4Cl$ (Scheme 4). Employing $D_2O$ instead of aqueous $NH_4Cl$ as the quenching agent led to α-deuterated ($\eta^6$-methyl phenylacetate)$Cr(CO)_3$ **24** in 95% yield. These results suggest that the Grignard reagents readily deprotonate the unsupported ester **3** to give enolate **23**, whereas addition is the primary reaction channel for the supported substrate. In addition to the possible influence of steric hindrance on the different behavior of **11** and **3**, one must also consider the impact of the electronic differences between a phosphine and a CO ligand.

**Scheme 4**



The resin-bound alcohols **13** and **14** were also found to be amenable to derivatization. As expected, treatment of alcohols **13** and **14** with an acetyl chloride/triethylamine mixture in the presence of DMAP led to the corresponding acetates **25** and **26** (Scheme 5).[10] Cleavage from the resin afforded free esters **25** and **26** in 80−86% yield based on **13** and**14** and 74−76% based on the nonsupported alcohols **5** and **6** (see Scheme 6).

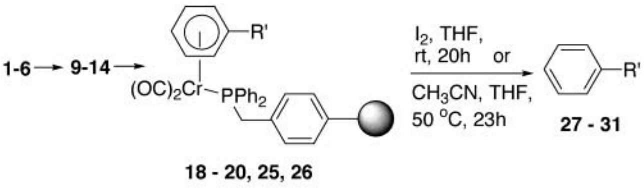
**Scheme 5**



**13** $\longrightarrow$ **25** $R' = (CH_2)_2OC(O)CH_3$

**14** $\longrightarrow$ **26** $R' = (CH_2)_3OC(O)CH_3$

**Scheme 6**



**18** $\longrightarrow$ **27** $R' = (CH_2)_2C(OH)(CH_3)C_2H_5$ 79%[a] (66%)[b]

**19** $\longrightarrow$ **28** $R' = CH_2C(OH)(C_2H_5)_2$ 76%[a] (61%)[b]

81%[a] (73%)[b]

**20** $\longrightarrow$ **29** $R' = (CH_2)_2C(OH)(C_2H_5)_2$ 82%[a] (78%)[b]

**25** $\longrightarrow$ **30** $R' = (CH_2)_2OC(O)CH_3$ 80%[a] (74%)[b]

**26** $\longrightarrow$ **31** $R' = (CH_2)_3OC(O)CH_3$ 86%[a] (76%)[b]

[a] Based on **9-14**

[b] Based on **1-6**

[a] Based on **9**−**14**. [b] Based on **1**−**6**.

Products **27**−**31** were released from the solid support by oxidative cleavage of the Cr-arene bond with iodine or simply by decomplexation with acetonitrile (Scheme 6). The spectra of **27**−**31** were identical to those described in the literature.[11] It must be noted, that the yields of the recovered products **27**−**31** based on resin-bound substrates **9**−**14** (76−86%) were comparable to those reported previously;[5] however, the yields obtained in the current work are fully *3-fold higher* than in previous reports when they were based on the original nonsupported precursors **1**−**6** (61−78%).

Although the frequently used iodine decomplexation method gave satisfactory results in this study, removal of excess iodine complicated the workup and resulted in decreased yields of final products **27**−**31**. To simplify the recovery protocol, an acetonitrile-assisted methodology was developed. As depicted in Scheme 6, the use of acetonitrile required slightly elevated temperature (50 °C); however, this approach may be the method of choice in solid-supported chemistry because of the ease of workup and higher final product yields.

The importance of combinatorial chemistry stems from the ability to rapidly generate a vast number of compounds. From this point of view, the linker formation technique described above could be applied to advantage in the realm

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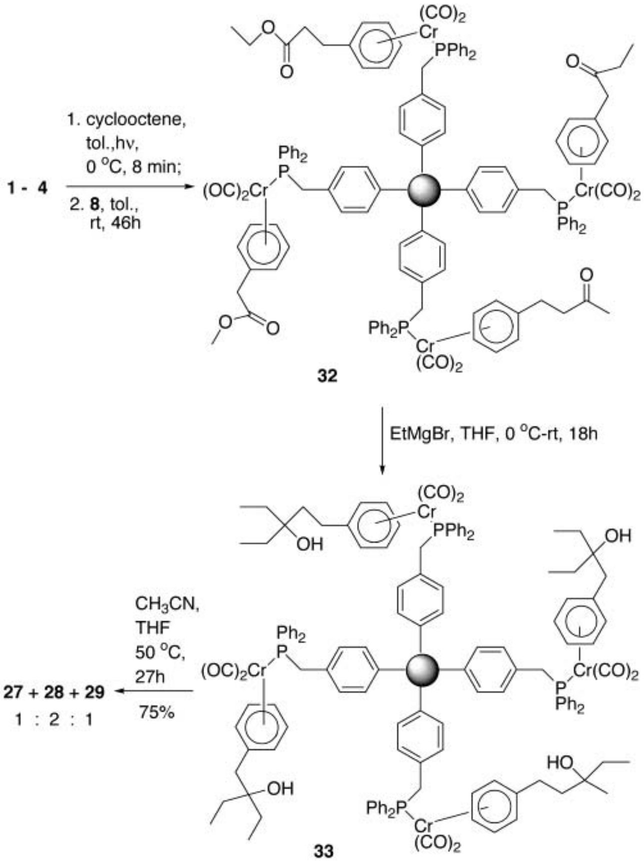
[9] (a) Negishi, E. In *Organometallics in Organic Synthesis*; Wiley: New York, 1980; Vol. 1. (b) Imamoto, T.; Takiyama. N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

[10] In addition to the chromium carbonyl stretching at 1887−1829 $cm^{-1}$, the IR spectra of **25** and **26** revealed absorptions at 1741 and 1737 $cm^{-1}$ that correspond to the C═O stretches of the acetates.

[11] (a) Wrobel, D.; Tacke, R.; Wanuagat, U.; Harder, U. *Chem. Ber.* **1982**, *115*, 1694. (b) Katritzky, A. R.; Qi, M. *J. Org. Chem.* **1997**, *62*, 4116. (c) Suzuki, N.; Rousset, C. J.; Aoyagi, K.; Kotora, M.; Takahashi, T. *J. Organomet. Chem.* **1994**, *473*, 117. (d) Patel, V. F.; Pattender, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2703. (e) Chandrasekhar, S.; Ramachandar, T.; Reddy, M. V.; Takhi, M. *J. Org. Chem.* **2000**, *65*, 4729.

**Scheme 7**



of combinatorial or parallel synthesis. This loading methodology allows for the simultaneous incorporation of a variety of starting materials onto the solid support. Therefore, considerable time could be saved in preparing and testing diverse libraries. A control experiment was conducted in order to determine if single-pot loading of numerous substrates onto the resin would be possible and to observe whether these multicomponent reagents would be amenable to further chemical manipulation. In the event, irradiation of equimolar quantities of **1**−**4** with excess cyclooctene in toluene followed by treatment with resin-bound phosphine **8** afforded the resin **32** containing four different substrates (Scheme 7).[12] The polymer-bound ketoester **32** was reacted with excess ethylmagnesium bromide to give the mixed polymeric alcohol **33**. The subsequent acetonitrile-assisted cleavage of the linker furnished a mixture of tertiary alcohols **27**, **28**, and **29** in a ratio of 1:2:1 (by $^1$H NMR spectroscopy) in an overall yield of 84% based on **32** and 75% based on a mixture of **1**−**4**.

In conclusion, a convenient and efficient protocol for making an arene-chromium carbonyl linker has been developed, and its utility in solid-phase synthesis was evaluated. This process displayed several useful attributes including high substrates loading (84−95%), high chemical yields, a simple recovery procedure, and multicomponent capabilities. The proposed methodology represents a valuable tool for accessing a variety of resin-bound products and could find broad application in the generation of combinatorial libraries.

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(12) The IR spectrum of **32** exhibited chromium carbonyl stretching frequencies at 1886 and 1831 cm$^{-1}$ and two bands at 1738 and 1721 cm$^{-1}$ corresponding to the ester and keto groups, respectively, which is consistent with the proposed structure.