Pergamon

Tetrahedron Letters 43 (2002) 7357–7360

TETRAHEDRON
LETTERS

# Synthesis of cyclopentadienylmanganese tricarbonyl resins as potential olefin traceless supports

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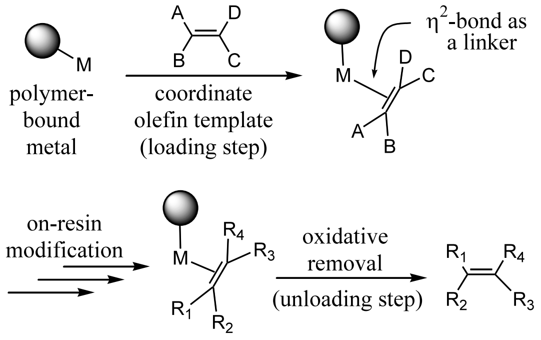
Received 17 June 2002; revised 15 August 2002; accepted 16 August 2002

**Abstract**—Cyclopentadienylmanganese tricarbonyl (cymantrene) was attached to polymer support via amide linkages. Two synthetic routes to obtain these cymantrene resins in high yield are reported. Spectroscopic evidence indicates that olefin substrates were loaded to give the corresponding $\eta^2$-complexes under light-promoted ligand exchange conditions by using a THF suspension of these manganese-containing resins. Subsequent treatment of the resin/olefin complex with mild oxidizing agents afforded the starting olefins in high purities.

Despite their importance as therapeutic agents, only a few methods are currently available for the solid-phase synthesis of olefin libraries.[1] Existing solid-phase olefin synthesis methods require that the alkene sacrifice one of its $\sigma$-bonds to form a link to the solid support, which usually limits the range of products that can be obtained. As an alternative, we envision that a functionalized olefin template can be attached *through its $\pi$-electrons* to an organometallic resin capable of coordinating carbon–carbon double bonds (Scheme 1).[2] Subsequent release of the olefin from the coordinating metallo-resin should return the double bond functional group leaving no trace of the linkage element. Metal carbonyl compounds are ideal in this regard since they are known to undergo $\eta^2$-coordination with double bonds via ligand substitution.

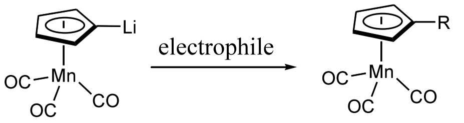
Among the various metal carbonyl compounds that may be used for the solid-phase $\eta^2$-coordination of olefins, cyclopentadienylmanganese tricarbonyl (cymantrene) stands out as a relatively stable, non-toxic, and environmentally friendly compound.[3] Importantly, the cymantrene/olefin bond has demonstrated stability towards a variety of bond-forming conditions,[4] and should prove useful as a solid-phase linker for the combinatorial synthesis of olefins.

We decided to pursue nucleophilic strategies involving lithio-cymantrene **1**[5] (Table 1) to synthesize manganese-containing resins. Initially we attempted to attach

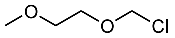


**Scheme 1.** Use of metallo-resins as olefin linkers.

**Table 1.** Derivatization of cymantrene



**1** **2a - e**

| entry | electrophile | % yield |
|---|---|---|
| a | TBS-Cl | 26 |
| b |  | 42 |
| c | PhCOCl | 59 |
| d | R—N=C=O R = Ph | 83 |
| e | R—N=C=O R = Bn | 89 |

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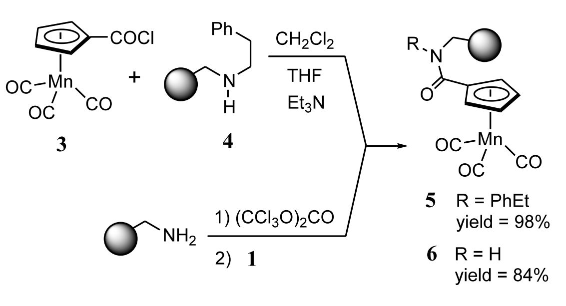
PII: S0040-4039(02)01726-4

cymantrene to polymer support via a C–C bond. However, our solution model studies as well as on-resin reactions involving benzyl halide derivatives with lithio-cymantrene **1** (not shown) led to unsatisfactory results. We also envisioned the attachment of cymantrene to polymer support via silyl-carbon, ether, ketone, and amide linkages.

Thus model studies involving the reaction of lithio-cymantrene **1** with *tert*-butyldimethylsilyl chloride (TBSCl), methoxyethoxymethyl chloride (MEMCl), benzoyl chloride, and two isocyanates were performed (Table 1).[6] The reaction of lithio-cymantrene **1** with TBSCl gave coupling product **2a** in low yields (Table 1). The reaction of **1** with methoxyethoxymethyl chloride (MEMCl) gave more promising results leading to adduct **2b** in 42% isolated yield.[7] The reaction of **1** with MEMCl suggests that cymantrene can potentially be attached to a variety of commercially available PEG-polystyrene resins that contain the alkoxymethyl chloride terminus. Good reactivity was also observed in the reaction of **1** with benzoyl chloride giving **2c** in 59% yield. Finally, lithio-cymantrene **1** reacts with phenyl and benzyl isocyanate to give amides **2d** and **2e** in excellent yields (80–90%). In contrast to cymantrene derivatives **2a**–**c**, products **2d** and **2e** were remarkably stable and could be easily recrystallized to give highly pure material on the gram scale.

Based on the stability of cymantrene amide derivatives **2d** and **2e**, we sought to prepare amide-linked cymantrene resins using two routes (Scheme 2). Our first approach involved an amide coupling reaction with cymantrene acid chloride **3**. In this approach, cymantrene acid chloride **3** was obtained from a precursor cymantrene carboxylic acid that was synthesized according to known methods.[5a] Acid chloride **3** was then reacted with amine resin **4** to give resin **5** in near-quantitative yields.[8] Although this cymantrene acid chloride approach gave resin **5** in excellent yields, we found it somewhat difficult to prepare large quantities of cymantrene carboxylic acid required for a large-scale synthesis of resin **5**.

In our second approach to the synthesis of an amide-linked cymantrene resin, we sought to take advantage of the high coupling yields of lithio-cymantrene **1** with phenyl and benzyl isocyanate observed in our solution-phase model studies. Following a literature procedure to prepare isocyanate resin from aminomethyl-polystyrene,[9] we developed a simple method to attach cymantrene on resin. (Scheme 2).[10]



**Scheme 2.** Attachment cymantrene to polymer support using an amide linkage.

Earlier reports[11] indicate that the UV irradiation of a THF solution of cymantrene leads to the substitution of one of the cymantrene carbonyls with THF.[12] This complex, which is deep red in color, readily coordinates olefins. We have studied the coordination of series olefins with cymantrene in the solution phase and have found that the complexation reaction is fairly general.[13]

Similar to the behavior of cymantrene in the solution-phase, the irradiation (254 nm) of a THF suspension of cymantrene resin **5** gives a deep red-color signifying the presence of THF complex **7** by analogy with related systems in the solution phase (Fig. 1). We found IR spectroscopic analysis to be very useful in determining the appropriate activation time necessary to convert resin **5** to its activated form **7**. An IR study of resin **5** irradiated with UV light (254 nm) for varying times indicates that the manganese carbonyl peak moved gradually towards the far-infrared by 8 units ($cm^{-1}$) over the course of 10 h (Fig. 1). Longer irradiation times did not appreciably alter the position of the manganese carbonyl peak. In contrast to the solution-phase activation of cymantrene, longer irradiation times were required for analogous activation of resin **5** (30 min versus 10 h). As in the solution-phase case, the treatment of resin **7** with olefins leads to yellow colored resins. An IR analysis of cymantene resin **5** coordinated with olefins indicated that the carbonyl absorption shifted back to higher wavenumbers (~2030 $cm^{-1}$).

Readily available benzalacetone (**8**) and 4-chlorostyrene (**9**) were chosen to examine the olefin-linking capability of resin **5** (Scheme 3). Our olefin loading protocol was as follows: cymantrene resin **5** (500 mg, 1.0 mmol/g)

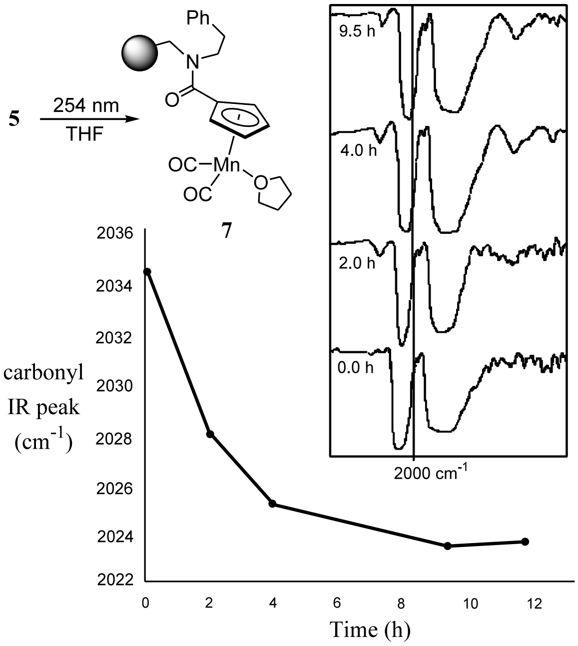
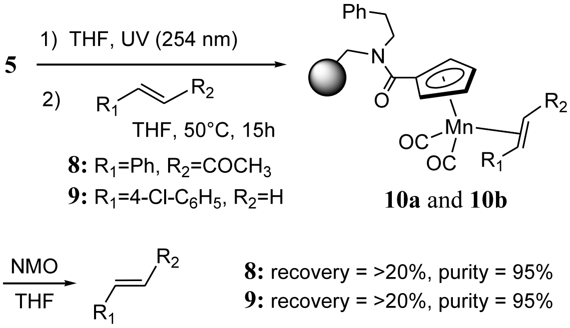


**Figure 1.** IR analysis of the light-assisted conversion of resin **5** to intermediate **7** at varying lengths of time.



**Scheme 3.** Attachment of alkenes to manganese resin **5** followed by unloading.

was added to a microfilter funnel (25 mL). The funnel was sealed and flushed with argon followed by the addition of THF (8 mL). The funnel was vibrated while irradiating with UV (254 nm) for 8 h to give activated resin **7**. Olefin was then added (1 mmol) and the funnel was vibrated at 50°C for 15 h. The resin suspension was filtered and the resin was washed with THF and MeOH and dried at 35°C/0.5 mmHg for 5 h to give **10a** and **10b** as yellow colored resins.

Attempts to recover olefins **8** and **9** from resins **10a** and **10b** were made using a variety of oxidative conditions such as $FeCl_3$, air sparging in MeCN, and NMO. Our current optimal conditions involve the use of NMO in THF for 12 h leading to a >20% recovery (Scheme 3). For both olefins **8** and **9**, the NMO procedure gave nearly pure olefins (95%) upon recovery once the NMO oxidant was removed by filtration through a plug of silica gel.[14]

In conclusion, two efficient methods to attach cymantrene to a polymer support via an amide linkage have been developed. We have also demonstrated that these manganese-containing resins can link olefins via $\eta^2$-bonding. In addition to other oxidative protocols, we are currently examining light-mediated methods to unload olefin from the manganese resin. We anticipate that the successful optimization of the loading and unloading steps should render this $\eta^2$-linker approach useful for the combinatorial synthesis of therapeutically interesting olefins.

## Acknowledgements

We are grateful to Eli Lilly and Company for a generous donation of equipment. Acknowledgement is also made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

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1. For recent examples of solid phase olefin synthesis, see: (a) Blaskovich, M. A.; Kahn, M. *J. Org. Chem.* **1998**, *63*, 1119; (b) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.* **1997**, *38*, 7143.
2. To our knowledge, this paper represents the first synthesis of organometallic resins capable of linking olefins through an $\eta^2$-bond. However, the use of polymer-based $\eta^6$-linkers involving chromium complexes for the synthesis of benzene derivatives has been reported: (a) Gibson, S. E.; Hales, N. J.; Peplow, M. A. *Tetrahedron Lett.* **1999**, *40*, 1417; (b) Semmelhack, M. F.; Hilt, G.; Colley, J. H. *Tetrahedron Lett.* **1998**, *39*, 7683.
3. Coates, G. E. *Organo-Metallic Compounds*; John Wiley & Sons: Now York, 1960.
4. Schinzer, D.; Blume, T.; Woltering, M. *Synlett* **1994**, 1045.
5. (a) Nesmeyanov, A. N.; Anisimov, K. N.; Kolobova, N. E.; Makarov, Y. V. *Izv. Akad. Nauk SSSR*, *Ser. Khim.* **1968**, *3*, 686; (b) Herberhold, M.; Biersack, M. *J. Organomet. Chem.* **1995**, *503*, 277.
6. All new cymantrene derivatives were characterized by $^1H$ NMR and IR.
7. A representative synthesis of **2b**: BuLi (1.6 M in hexane, 1.5 mmol) was added dropwise over a period of 10 min to a −42°C THF (7 mL) solution of $CpMn(CO)_3$ (0.75 mmol). After the mixture was stirred for 1 h, methoxyethoxymethyl chloride (2.25 mmol) was added via syringe. The reaction was allowed to proceed for 6 h while the temperature was gradually increased to room temperature. The solvent was removed and the residue was subjected to column separation (silica gel, 6:4 hexane:EtOAc) leading to 93.1 mg (42%) of **2b** as an oil. $^1H$ NMR (500 MHz, $CDCl_3$) 4.76 (d, 4H, Cp, $J = 77.5$ Hz), 4.15 (s, 2H, $CpCH_2$), 3.65–3.57 (m, 4H, $CH_2CH_2$), 3.39 (s, 3H, $CH_3$).
8. A general procedure for the synthesis of resin **5** is as follows: Merrifield's resin (1.5 mmol/g) was refluxed in THF with excess phenethyl amine in the presence of $Et_3N$ for 2 days to give amine resin **4** (1.32 mmol/g) in theoretical loading yield after copious washing. The resin was then suspended in $CH_2Cl_2$ in a sealed flask and flushed with argon in preparation for the reaction with cymantrene acid chloride **3**. In another flask, cymantrene acid (1.5 equiv.) was added and the flask was capped with a rubber septum, flushed by argon, wrapped in aluminum foil and attached to a bubbler. THF was added to dissolve the acid followed by $SOCl_2$ (5 equiv.). After stirring for 1 h, excess $SOCl_2$ and solvent were quickly removed in vacuo at room temperature leading to a yellow solid which was placed under an argon atmosphere. The solid was then dissolved in $CH_2Cl_2$ and transferred to the vessel containing the amine resin via syringe. Excess $Et_3N$ (>5 equiv.) was added and the flask was vibrated for 1 h. Liquid was filtered off and the resin was washed with THF, MeOH, $H_2O$, MeOH, THF, $CH_2Cl_2$ and MeOH successively. It was then dried in vacuo to give cymantrene resin **5** in 98% loading yield (1.0 mmol/g).
9. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882.
10. A general procedure for the synthesis of resin **6** is as follows: triphosgene (1.7 equiv.) was added to aminomethyl polystyrene (1.46 mmol/g) suspended in dry $CH_2Cl_2$. The mixture was cooled to −42°C followed by the addition of excess $Et_3N$ (5 equiv.). The resulting

mixture was rotated for 24 h at room temperature. It was then washed with $CH_2Cl_2$ and THF successively. Lithiocymantrene **1** (2 equiv.) prepared from $CpMn(CO)_3$ and *t*-BuLi was then transferred to isocyanate resin that was pre-cooled to −42°C. The mixture was then vibrated for 10 h at −42°C, neutralized, washed with $CH_2Cl_2$ and THF successively, and dried in vacuo to give a yellow-colored cymantrene resin in 84% loading yield (0.94 mmol/g).

11. (a) Yan, B.; Kumaravel, G.; Anjaria, H.; Wu, A.; Petter, R. C.; Jewell, C. F.; Wareing, J. R. *J. Org. Chem.* **1995**, *60*, 5736; (b) Adams, D. M.; Squire, A. *J. Organomet. Chem.* **1973**, *63*, 381.
12. We found that the light-mediated CO–THF exchange of cymantrene can be executed in common glassware using a low-watt UV (365 nm) lamp. The reaction process can be monitored by the appearance of a deep-red color. Using a UV–vis spectrometer, we determined that the red color reached its greatest intensity after 30 min of irradiation in our setup.
13. We examined the coordination of methyl 1-cyclohexene-1-carboxylate, 1-phenyl-1-hexene, benzalacetone, *trans*-styrylacetic acid, crotyl chloride, 3-bromo-3-buten-1-ol, *cis*-4-chloro-2-butenylamine hydrochloride, 4-chlorostyrene, 2-cyclopenten-1-one and 2-cyclohexen-1-one on $CpMn(CO)_3$. All led to positive results except *cis*-4-chloro-2-butenylamine hydrochloride due to solubility problems. A representative procedure for the synthesis of $CpMn(CO)_2(p\text{-}ClPhCH{=}CH_2)$ (a new compound) is illustrated below: a vial containing $CpMn(CO)_3$ (204 mg, 1 mmol) was sealed and flushed by argon for 10 min. THF (15 mL) was added via syringe. The resulting solution was irradiated by UV (365 nm) for 30 min while stirring. The red solution was then purged by argon for 2 min and 4-chlorostyrene (178 μL, 1.5 mmol) was added via syringe. During the course of 4 h, the reaction vessel was irradiated the first 10 min of each hour. The solvent was removed in vacuo and the residue was purified using preparative TLC leading to 110 mg (35%) of $CpMn(CO)_2(p\text{-}ClPhCH{=}CH_2)$ as a yellow solid: $^1H$ NMR (500 MHz, $CDCl_3$) 7.15 (d, 2H, Ph, $J=6.5$ Hz), 6.95 (d, 2H, Ph, $J=6.5$ Hz), 4.47 (s, 5H, Cp), 4.10 (m, 1H, $CH{=}CH_2$), 2.81 (m, 1H, $CH{=}CH_2$), 2.74 (m, 1H, $CH{=}CH_2$); IR (KBr) 1947, 1888, 1508, 1484, 1431, 1092, 826. $CpMn(CO)_2(p\text{-}ClPhCH{=}CH_2)$ decomposes upon extended air exposure especially when in solution.
14. The purity of recovered olefins **8** and **9** was determined by comparison (using NMR and HPLC) with the authentic commercially available compound. HPLC determinations were made using $C_{18}$ column. Benzalacetone and 4-chlorostyrene peaks appeared at 6.89 and 9.89 min, respectively, using the following elution gradient: 1 mL/min starting with 50% $CH_3CN$ in $H_2O$ and ending with 80% $CH_3CN$ in $H_2O$ over the course of 25 min.