Pergamon

Tetrahedron Letters 40 (1999) 2251–2254

TETRAHEDRON LETTERS

Alkylation of (η^6-Arene) - Ru(II) Complexes: Construction of Benzylic Quaternary Carbon Centers

F. Christopher Pigge,* Shiyue Fang, Nigam P. Rath

Department of Chemistry, University of Missouri-St. Louis, St. Louis, Missouri 63121-4499

Received 10 December 1998; revised 12 January 1999; accepted 14 January 1999

Abstract: Both *endo*- and *exo*-(η^6-1,4-dimethyltetrahydroquinoline)Ru(II)Cp·PF_6 complexes were found to undergo alkylation at the benzylic position upon treatment with NaH and an electrophile. The resulting benzylic quaternary carbon center was formed by reaction of the electrophile exclusively from the face opposite the CpRu(II) fragment regardless of the stereochemistry present in the starting complex. The stereoisomeric Ru(II) complexes of 1,3-dimethylindoline exhibit similar reactivity.

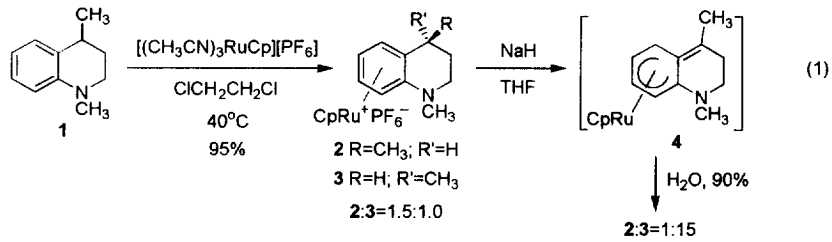
Organometallic complexes of the type (η^6-arene)ML_n are well-recognized as valuable intermediates in organic synthesis as a consequence of the facility with which the aromatic ligand can be functionalized. η^6-Arene tricarbonyl chromium complexes serve as the prototypical example for this family of compounds and useful synthetic procedures which exploit the susceptibility of the coordinated ring to undergo substitution by reaction with nucleophiles[1a] and ring deprotonation[1b] have been developed. The chromium moiety also enhances the acidity of benzylic hydrogens in addition to acting as a stereodirecting element, hence providing a means for the stereocontrolled manipulation of sites adjacent to the coordinated arene nucleus.[1c,d] In contrast, the chemistry of isoelectronic (η^6-arene)Ru(II)Cp^+ (Cp=cyclopentadienyl) complexes has received comparatively little attention, in spite of the mild conditions under which these complexes can be prepared and the observation that the cationic nature of these materials results in a more activated arene ligand. Indeed, nucleophilic aromatic substitution reactions of Ru-coordinated halo- and nitroarenes proceed under extremely mild conditions to afford functionalized substrates inaccessible *via* Cr-based methodology.[2] The activating effect exerted by the CpRu(II) moiety also should be manifested at positions conjugated to the arene ligand (benzylic and homobenzylic); however, manipulation of side-chain functionality has been limited to reports describing a few reactions (*e.g.*, conjugate addition,[3a] hydrogenation,[3b] Diels-Alder cycloaddition[3b]) of the C=C in "styrene-type" ligands.

It is well-known that benzylic functionalizations of (η^6-arene)$Cr(CO)_3$ complexes which involve deprotonation-alkylation sequences occur with high levels of stereoselection.[1c,d] In general, only benzylic hydrogens oriented *anti* to the $Cr(CO)_3$ fragment (*i.e.*, *exo*) are susceptible to deprotonation. Electrophilic reactants approach the resulting Cr-stabilized carbanions from the sterically less-hindered *exo* face to provide the substituted products.[4] Benzylic hydrogens that are constrained to project toward the *endo* face of these complexes are unreactive. Benzylic alkylations of (η^6-arene)Ru(II)Cp^+ complexes, however, may not be limited by the requirement of an *exo*-oriented benzylic hydrogen owing to the enhanced reactivity of the coordinated arene. While reports which describe the benzylic per-alkylation of certain structurally related (η^6-arene)Fe(II)Cp cations have appeared,[5] side-chain alkylation reactions of arene - Ru(II) complexes have not been examined. It is noteworthy that complete alkylation of benzylic positions in such complexes may offer a potentially general

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00218-X

method for construction of benzylic quaternary carbon centers, and the present study was designed to address the viability of this approach for accessing this important structural motif.[6]

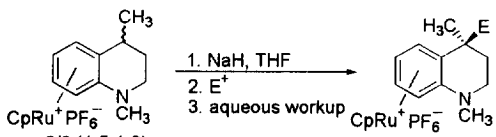
At the outset, an arene ligand which would permit one to assess not only the reactivity of *exo*- and *endo*-oriented benzylic hydrogens but also the stereoselectivity of subsequent alkylations was desired. Consequently, the CpRu(II) complex of 1,4-dimethyltetrahydroquinoline (**1**)[7] was prepared (Eq. 1).



(1)

Complexation was effected in high yield by treatment of the arene with $[(CH_3CN)_3RuCp][PF_6]$ in accordance with literature procedures.[8] The resulting complex was isolated as a 1.5:1.0 mixture of stereoisomers (**2/3**) epimeric at C4.[9,10] Without separation, the isomeric mixture was subjected to conditions expected to result in benzylic deprotonation (NaH, THF, reflux, 12 h). Under these conditions, the relatively insoluble complex gradually dissolved with concomitant production of a golden-yellow solution, presumably indicative of formation of the neutral species **4**. Quenching of the reaction with H_2O led to 90% recovery of the starting complex, now present as a 1:15 mixture of isomers favoring the *endo*-methyl derivative **3**. Thus, it appears the *endo*-oriented benzylic hydrogen present in the conformationally rigid CpRu(II) complex **2** is indeed susceptible to deprotonation.

Next, the reactivity of putative intermediate **4** toward a variety of organic electrophiles was examined (Eq. 2). In each case, **4** was generated under the conditions described above followed by addition of a slight



(2)

E^+= Br–CH$_2$–Ph	E = CH_2Ph	(**5**, 91%)
Br–CH$_2$–CH=CH$_2$	$CH_2CH{=}CH_2$	(**6**, 75%)
Br–CH$_2$–CH=C(CH$_3$)$_2$	$CH_2CH{=}C(CH_3)_2$	(**7**, 91%)
Br–CH$_2$–C(CH$_3$)=CH$_2$	$CH_2C(CH_3){=}CH_2$	(**8**, 52%)
Br–CH$_2$–C≡CCH$_3$	CH_2CCCH_3	(**9**, 60%)
ClC(O)OCH$_3$	$C(O)OCH_3$	(**10**, 54%)
Ac_2O	$C(O)CH_3$	(**11**, 71%)
Br–CH$_2$–CH$_3$	CH_2CH_3	(**12**, 36%)

excess of the electrophile and continued reflux for 1 h. After addition of H_2O, the THF was evaporated and NH_4PF_6 was added to the remaining aqueous residue. Extraction of the mixture with CH_2Cl_2 followed by addition of Et_2O resulted in precipitation of the products, which were isolated by suction filtration as white to yellow air- and moisture-stable solids. In some cases, a small amount of unreacted starting material was present in the crude product and recrystallization from CH_2Cl_2/Et_2O was necessary to obtain spectroscopically homogeneous materials. Each electrophile examined afforded functionalized Ru(II) complexes possessing a quaternary benzylic center in yields ranging from good to excellent.[10] Significantly, complexes **5-12** were obtained as *single stereoisomers* in which the newly generated quaternary centers were formed by approach of the electrophile exclusively from the face opposite the metal. Stereochemical assignments were made on the basis of 2D NOE experiments, which revealed a correlation between the Cp hydrogens and the hydrogens on the *endo* C4 methyl substituent. Further support for this stereochemical assignment was provided by single-crystal X-ray analysis of acetyl-substituted complex **11** (Figure 1).[11]

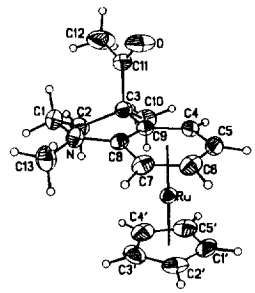
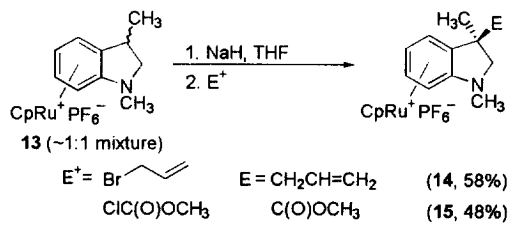


***Figure 1** Molecular structure of complex 11 (PF_6 counterion omitted for clarity)*

Using a similar reaction sequence, 1,3-dimethylindoline[12] complex **13** (obtained as a ~1:1 mixture of *endo* and *exo* isomers)[10] also was found to undergo stereoselective benzylic alkylation with the two electrophiles examined thus far (Eq. 3). It is interesting to note that benzylic deprotonation of

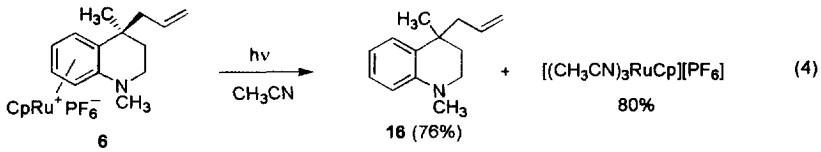


(3)

(indoline)$Cr(CO)_3$ complexes has been reported to result in electrocyclic opening of the five-membered ring.[13] Products arising from such a process were not detected in this study.

Finally, an important consideration in synthetic procedures involving (η^6-arene)-metal complexes is the ease with which the aromatic ligand can be liberated from the metal center. With respect to the Ru(II) complexes used in this study, decomplexation can be effected under mild photolytic conditions which permit isolation of the metal-free arene as well as recovery of the CpRu(II) fragment in a reusable form. To illustrate this point, an acetonitrile solution of complex **6** was irradiated overnight at rt in a Rayonet photochemical

apparatus in accordance with literature procedures[8] to afford tetrahydroquinoline derivative **16** as a colorless oil and $[(CH_3CN)_3RuCp][PF_6]$ as a yellow solid in isolated yields of 76% and 80%, respectively (Eq. 4).



In conclusion, this study demonstrates the feasibility of stereoselectively constructing benzylic quaternary carbon centers *via* alkylation of (η^6-arene)Ru(II)Cp cations. The ease of preparation coupled with decomplexation methods which allow for the recovery of the CpRu(II) fragment, and the enhanced reactivity exhibited by coordinated arene ligands, render these materials attractive synthetic intermediates relative to other arene - metal complexes. Current efforts are focused on optimizing and extending the scope of this methodology to include functionalization of a variety of arene ligands with a range of electrophilic reaction partners. In addition, intramolecular variations may provide concise, stereocontrolled routes to structurally elaborate polycyclic compounds. Potentially, optically pure planar-chiral (arene)Ru(II) complexes could be used to facilitate construction of quaternary carbon centers with control of absolute stereochemistry.

Acknowledgements: Financial support for this work was provided by the donors of the Petroleum Research Fund, administered by the American Chemical Society (ACS-PRF# 32756-G1), the University of Missouri Research Board, and the Department of Chemistry, University of Missouri - St. Louis. Acknowledgement is made to Dr. Janet Braddock-Wilking for her assistance in obtaining ^{1}H-^{1}H-NOESY spectra. Support for departmental instrumentation facilities (NMR and X-ray) was provided by grants from the NSF (CHE-9318696 and CHE-9309690) and the U. S. Department of Energy (DE-FG02-92-CH10499).

References and Notes

1. a) Semmelhack, M. F. *Comprehensive Organometallic Chemistry II* Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds., Elsevier Science Ltd., Oxford, UK, 1995, vol. 12, p. 979. b) Semmelhack, M. F. *Comprehensive Organometallic Chemistry II* Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds., Elsevier Science Ltd., Oxford, UK, 1995, vol. 12, p. 1017. c) Davies, S. G.; McCarthy, T. D. *Comprehensive Organometallic Chemistry II* Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds., Elsevier Science Ltd., Oxford, UK, 1995, vol. 12, p. 1039. d) Davies, S. G.; Coote, S. J.; Goodfellow, C. L. *Advances in Metal-Organic Chemistry* Liebeskind, L. S., Ed., JAI Press Ltd., 1991, vol. 2, p. 1.
2. a) Pearson, A. J.; Chelliah, M. V. *J. Org. Chem.* **1998**, *63*, 3087 and references therein. b) Janetka, J. W.; Rich, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 6488. c) Gill, U. S.; Moriarty, R. M.; Ku, Y. Y.; Butler, I. R. *J. Organomet. Chem.* **1991**, *417*, 313 and references therein.
3. a) Moriarty, R. M.; Enache, L. A.; Gilardi, R.; Gould, G. L.; Wink, D. J. *Chem. Commun.* **1998**, 1155. b) Glatzhofer, D. T.; Liang, Y.; Funkhouser, G. P.; Khan, M. A. *Organometallics* **1994**, *13*, 315.
4. For an apparent exception to this general observation, see: Brisander, M.; Caldirola, P.; Johansson, A. M.; Hacksell, U. *J. Org. Chem.* **1998**, *63*, 5362.
5. Grundy, S. L.; Sam, A. R. H.; Stobart, S. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1663.
6. For recent reviews concerning the synthesis of quaternary carbon centers, see: a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 388. b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.
7. Gribble, G. W.; Heald, P. W. *Synthesis* **1975**, 650.
8. Gill, T. P.; Mann, K. R. *Organometallics* **1982**, *1*, 485.
9. The stereoisomeric ratio was easily determined from the ^{1}H-NMR spectrum.
10. All new compounds exhibited spectral (^{1}H-NMR, ^{13}C-NMR, IR) and analytical (combustion analysis) data consistent with the assigned structures.
11. All crystallographic data will be deposited with the Cambridge Crystallographic Database.
12. Gribble, G. W.; Hoffman, J. H. *Synthesis* **1977**, 859.
13. Dickens, P. J.; Slawin, A. M. Z.; Widdowson, D. A.; Williams, D. J. *Tetrahedron Lett.* **1988**, *29*, 103.