ORGANIC LETTERS

2009
Vol. 11, No. 18
4108−4110

Leaving Group Potential of a Substituted Cyclopentadienyl Anion Toward Oxidative Addition

Ethan L. Fisher and Tristan H. Lambert*

Department of Chemistry, Columbia University, New York, New York 10027

tl2240@columbia.edu

Received July 13, 2009

ABSTRACT

The facility with which a substituted cyclopentadienyl anion may function as a leaving group for palladium-catalyzed allylation reactions is demonstrated. Reaction of several allylcyclopentadienyl substrates is shown. Nucleophilic displacement of carbon with nitrogen is achieved in the deallylation of allylpenta-*p*-acetylphenylcyclopentadiene with *N*-methylbenzylamine.

The ability of certain chemical species to function as leaving groups (nucleofuges) is fundamental to all nucleophilic substitution and elimination reactions (Figure 1).[1] The nucleofugal proficiency of a given species scales directly with its capacity to accommodate two electrons from a heterolytically cleaved bond. Because of this correlation, leaving groups usually take the form of highly stabilized anions like halides or sulfonates or neutral species such as water, alcohols, or amines. By the same token, carbon is not commonly found to serve the role of leaving group, especially for nucleophilic substitution reactions, due to the general lack of C−C bond polarization and the normally high instability of the resultant carbanions.[2] In cases where a carbon center does serve as a leaving group (e.g., retro-aldol, haloform reaction), the nucleofugal electron pair is usually stabilized via resonance or induction by more highly electronegative atoms. On the other hand, alternative carbon moieties should be able to function as efficient leaving groups provided their corresponding anions are rendered sufficiently stable. Importantly, identification of a general carbon-based leaving group scaffold could facilitate the invention of a number of powerful new reaction methods involving nucleophilic substitution or elimination mechanisms. Especially intriguing is the fact that, in contrast to traditional leaving groups such as the halides, carbon may be stereogenic, leading to the possibility of inventing novel asymmetric reactions using chiral nucleofugal carbon fragments. Motivated by these possibilities, we have set as our goal the identification of a versatile and efficient carbon leaving group scaffold.

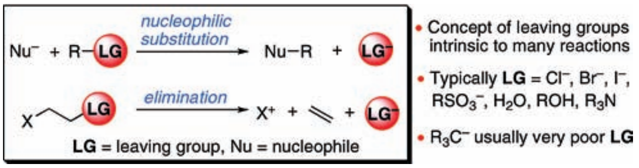


Figure 1. Leaving groups in organic chemistry.

In this regard, our attention has been drawn to cyclopentadienyl (Cp) anions, which are readily available in achiral

---

(1) Lepore, S. D.; Mondal, D. *Tetrahedron* **2007**, *63*, 5103.

(2) (a) Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1985**, *50*, 5415. (b) Weiss, R.; Huber, S. M.; Pühlhofer, F. G. *Eur. J. Org. Chem.* **2005**, 3530. (c) Mattioli, M.; Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1988**, *53*, 1087. (d) Cardellicchio, C.; Fracchiolla, G.; Naso, F.; Tortorella, P.; Holody, W.; Pietrusiewicz, K. M. *Tetrahedron Lett.* **1999**, *40*, 5773. (e) Cardellicchio, C.; Iacuone, A.; Naso, F.; Tortorella, P. *Tetrahedron Lett.* **1996**, *37*, 6017. (f) Bonesi, S. M.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 10022. (g) Garner, C. M.; Fisher, H. C. *Tetrahedron Lett.* **2006**, *47*, 7405.

10.1021/ol901598n CCC: $40.75

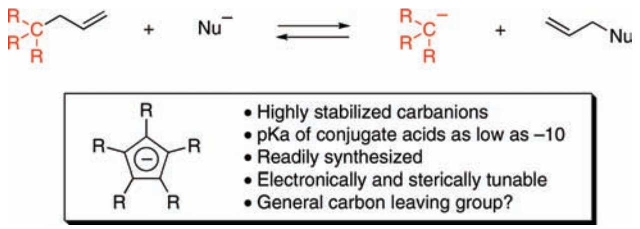


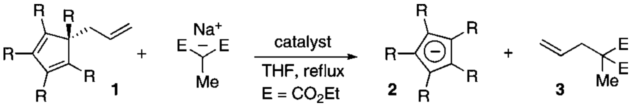
Figure 2. Carbon as a leaving group.

and chiral forms[3] and are highly tunable in regard to their electronic properties.[4] Importantly, the 6π-electron aromatic character of Cp anions lends to them remarkably high stability for carbanionic species. We were particularly intrigued by the fact that ring substitution can further enhance the stability of Cp anions to a remarkable extent,[5] such that the pK_a values of their conjugate acids (cyclopentadienes) are known as low as −11.[6] The possibility of such extraordinary carbanion stability led us to wonder whether an appropriately substituted Cp fragment could serve as an efficient leaving group for reaction processes such as nucleophilic substitution (Figure 2).

As an initial investigation of this concept, we decided to examine palladium-catalyzed allylation (Tsuji−Trost[7] reaction) using allylcyclopentadienes. Notably, the ability of malonate[8] and 1,3-diketone[9] moieties to serve as leaving groups for π-allyl palladium formation has been demonstrated and thus provides a useful benchmark by which to gauge the relative reactivity of Cp systems in this regard.[10]

In our initial experiments, we found that allylpentaphenylcyclopentadiene **1** (R = Ph) was unreactive to the sodium salt of diethyl methylmalonate in the presence of 20 mol % $Pd(PPh_3)_4$ in refluxing THF over prolonged periods of time (Table 1, entry 1). On the other hand, allylpenta-*p*-acetylphenylcyclopentadiene **1** (R = *p*-AcPh)[11] reacted quantitatively under the same conditions in only 15 min to produce methyl allyl malonate **3** along with the Cp anion **2** (entry 2). Catalyst loadings for this transformation could be decreased to 10 or 5 mol % without sacrificing yield and with reasonable scaling of reaction time (entries 3 and 4). No reaction was observed in the absence of palladium catalyst (entry 5).

Table 1. Optimization of Pd(0)-Catalyzed Nucleophilic Displacement of a Cyclopentadienyl Anion[a]



entry	R	catalyst	mol %	time	% convn
1	Ph	$Pd(PPh_3)_4$	20	24 h	<5
2	*p*-AcPh	$Pd(PPh_3)_4$	20	15 min	100
3	*p*-AcPh	$Pd(PPh_3)_4$	10	40 min	100
4	*p*-AcPh	$Pd(PPh_3)_4$	5	90 min	100
5	*p*-AcPh	--	--	24 h	<5

[a] Conversion determined by ^1H NMR using Bn_2O as an internal standard.

The results shown in Table 1 demonstrate the capacity of a cyclopentadienyl ring system to serve as a facile leaving group for oxidative addition to an unstrained allylic carbon−carbon bond. In comparison,[12] it appears that the Cp anion **2** is a more efficient leaving group than the malonate anion[8] and is comparable to a cyclic 1,3-diketone.[9a,c]

To further examine this process, we have investigated the transformations shown in Table 2.[13] Thus allyl, methallyl, and cinnamyl Cp substrates participate in the allyl transfer reaction with good to high efficiency (entries 1−3). Interestingly, the corresponding crotyl substrate was unreactive under these conditions (entry 4). On the other hand, a crotonate ester substrate was found to react efficiently and with no complications arising from Michael addition (entry 5). Cyclopentadienyl displacement with an alternative carbon nucleophile in the form of an acetoacetic ester also proved possible (entry 6). In accordance with the relative stabilities of the corresponding Cp anions, allylpenta-*p*-acetylphenylcyclopentadiene could be transformed to allylpentaphenylcyclopentadiene with complete conversion and high isolated yield (entry 7). Most interestingly, we found that a carbon−carbon bond could be replaced with a carbon−nitrogen bond with the use of *N*-benzylmethylamine as the nucleophile and 50 mol % palladium catalyst (entry 8). The reaction in this case appears to produce an equilibrium mixture of *N*-allyl and *C*-allyl products.

As a demonstration of this point, we conducted the following experiment. Thus, allylamine **7** was subjected to penta-*p*-acetylphenylcyclopentadiene **6** in the presence of 50 mol % $Pd(PPh_3)_4$ and Cs_2CO_3 in refluxing THF (Figure 3).

---

(3) For a review, see: Halterman, R. L. *Chem. Rev.* **1992**, *92*, 965.

(4) Rybinskaya, M. I.; Korneva, L. M. *Russ. Chem. Rev. (Engl. Transl.)* **1971**, *40*, 247.

(5) For example: (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 632. (c) Laganis, E. D.; Lemal, D. M. *J. Am. Chem. Soc.* **1980**, *102*, 6633.

(6) (a) Webster, O. W. *J. Am. Chem. Soc.* **1966**, *88*, 3046. (b) Vianello, R.; Maksic, Z. B. *Tetrahedron* **2005**, *61*, 9381.

(7) For recent reviews, see: (a) Lu, Z.; Ma, S. *Angew Chem. Int. Ed.* **2007**, *47*, 258. (b) Trost, B. M.; Lee, C. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 593−649. (c) Pfaltz, A.; Lautens, M. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, Germany, 1999; pp 833−886.

(8) Nilsson, Y. I. M.; Andersson, P. G.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1993**, *115*, 6609.

(9) (a) Vicart, N.; Goré, J.; Cazes, B. *Tetrahedron* **1998**, *54*, 11063. (b) Bricout, H.; Carpentier, J.-F.; Mortreux, A. *Tetrahedron Lett.* **1997**, *38*, 1053. (c) Vicart, N.; Goré, J.; Cazes, B. *Synlett* **1996**, 850.

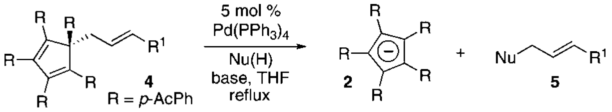
(10) Crabtree has reported the insertion of an iridium(I) complex to alkyl-substituted cyclopentadienes. (a) Crabtree, R. H.; Dion, R. P. *J. Chem. Soc., Chem. Commun.* **1984**, 1260 See also. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245.

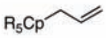
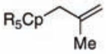
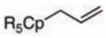
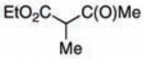
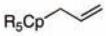
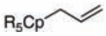
(11) For the synthesis of penta-*p*-acetylphenylcyclopentadiene: Lowack, R. H.; Volhardt, K. P. C *J. Organomet. Chem.* **1994**, *476*, 25.

(12) Bäckvall reported that the equilibration of monoallylic malonates required 24 h at 65 °C in THF (ref 8), while Cazes reported that conversion of 2-allyl-2-methyl-1,3-cyclopentanedione to diethyl allylmalonate in the presence of diethyl sodiomalonate and 5 mol % $Pd(PPh_3)_4$ in THF at 50 °C required 2.5 h (refs 9a and 9c).

(13) No other allyl products were isolated which would account for the loss of mass balance in these reactions.

Table 2. Optimization of Pd(0)-Catalyzed Nucleophilic Displacement of a Cyclopentadienyl Anion[a]



entry	substrate	Nu(H)	base	time (h)	% yield
1		$(EtO_2C)_2CHMe$	NaH	1.5	80
2		$(EtO_2C)_2CHMe$	NaH	4	71
3		$(EtO_2C)_2CHMe$	NaH	4	70
4		$(EtO_2C)_2CHMe$	NaH	> 6	0
5		$(EtO_2C)_2CHMe$	NaH	3	71
6			NaH	3	78
7		Ph_5CpH	n-BuLi	3	77
8[b],[c]		BnNHMe	Cs_2CO_3	3	69

[a] Reactions were performed by adding a solution of the nucleophile (1.5 equiv) and base (1.5 equiv) in THF to a solution of substrate (1 equiv) and $Pd(PPh_3)_4$ (5 mol %) in THF (0.03 M final concentration) and heating for the designated time. [b] 50 mol % $Pd(PPh_3)_4$ was used. [c] Yield determined by ^{1}H NMR with Bn_2O as an internal standard.

The result observed after 3 h was a 69:31 mixture of allyl amine **7** and allyl Cp **1**, a ratio identical to that observed when **1** was treated with benzylmethylamine under the same conditions (Table 2, entry 8). Presumably, the amine **7** is sufficiently basic to deprotonate Cp **6** to generate ammonium ion **8**, which is then activated toward metal insertion.[14]

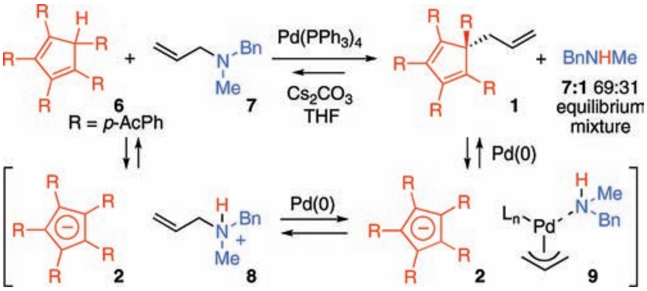


Figure 3. Equilibration of the allyl amine substrate.

In conclusion, we have demonstrated that a suitably substituted cyclopentadienyl moiety can function as a facile leaving group for metal-catalyzed substitution reactions. We believe that the broad electronic tunability and potential for chirality of the Cp framework raise intriguing possibilities for the development of a diverse menu of novel methodologies that rely on nucleofugal carbon expulsion. Currently, we are examining the leaving group potential of the cyclopentadienyl system in other contexts and exploring the development of asymmetric methods that employ chiral carbon leaving groups.

Supporting Information Available: Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901598N

---

(14) Selected examples of palladium insertion to allyl amines: (a) Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109. (b) Murahashi, S.-I.; Imada, Y.; Nishimura, K. *Tetrahedron* **1994**, *50*, 453. (c) Lemaire-Audoire, S.; Savignac, M.; Genêt, J. P. *Tetrahedron Lett.* **1995**, *36*, 1267.