COMMUNICATION

ChemComm
www.rsc.org/chemcomm

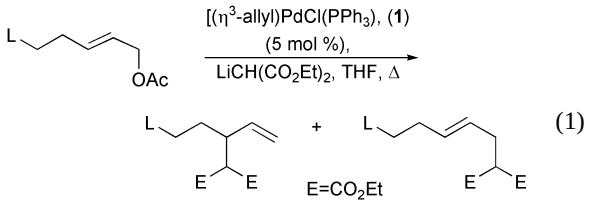
Palladium-catalyzed, heteroatom assisted, regioselective cyclizations

Marie E. Krafft* and Matthew C. Lucas
Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306, USA.
E-mail: mek@chem.fsu.edu; Fax: 850-644-8281; Tel: 850-644-2297

Received (in Corvallis, OR, USA) 27th February 2003, Accepted 1st April 2003
First published as an Advance Article on the web 6th May 2003

Unusual Pd-catalyzed cyclizations of unsymmetrical allylic acetates, where the nucleophile is tethered to the central allyl carbon, are shown for the first time to be remarkably controlled by heteroatom-mediated preassociation of the reacting partners.

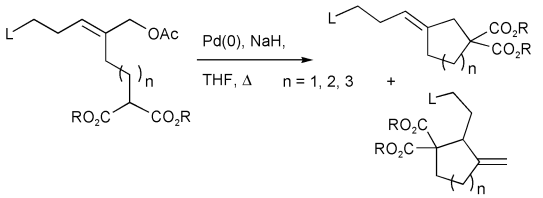
Formation of a π-allylpalladium complex by the oxidative addition of an allylic acetate to Pd(0) and subsequent reaction with a soft nucleophile has proved to be a powerful synthetic transformation.[1,2] In cases where the π-allylpalladium complex is unsymmetrical, two different regiochemical outcomes are possible, and commonly a mixture of two isomers is formed. Various factors influence regioselectivity, including steric bulk at the allylic termini,[3] polarizing functional groups adjacent to the complex,[4–7] and electronic and steric ligand effects.[8,9] Often these provide a partial solution to the regiochemical issue. In an earlier report, our group demonstrated for the first time that a homoallylic tertiary amine or thioether tethered to an allylic acetate directed addition of malonate to the allylic terminus proximal to the heteroatom (eqn. 1) *via* preassociation of reacting partners.[10] We later reported that alkenes also acted as directing groups in these alkylations.[11] Our previous observations have since been expanded by Yoshida *et al*. to include a removable 2-PyMe$_2$Si directing group.[12] We proposed that chelation of the tertiary amine, thioether, or olefin prior to bond formation played an integral role in determining regiochemical outcome. The directing effect overcame the normally strong steric bias and reaction occured at the more substituted terminus of even a monofunctionalized π-allyl moiety.



L = NMe_2	76 %	95	:	5
L = SMe	87 %	91	:	9

(1)

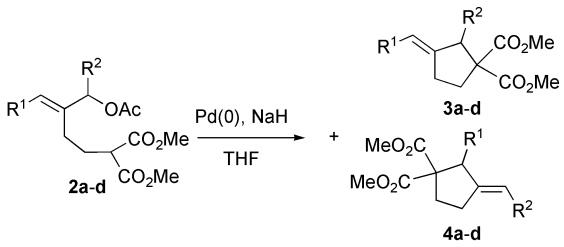
We anticipated that the intramolecular allylic substitution by a soft nucleophile to form a carbocycle would also be greatly influenced by such groups capable of promoting preassociation of reacting partners. The regiochemistry of Pd-catalyzed cyclizations is defined by the size of the newly forming ring when the nucleophile is tethered to the π-allyl terminus. Cyclizations where the nucleophile is tethered to the central π-allyl carbon are rather unusual and have only been carried out with symmetrical allyl complexes.[13] Herein we describe the first regioselective, Pd-catalyzed, cyclizations of unsymmetrical allylic acetates, to furnish five-, six- and seven-membered carbocycles (eqn. 2),[14] where heteroatom coordination, rather than ring size or steric interactions, was the dominant product determining factor. These examples illustrate the remarkable power of a directing group in imparting significant control over the regiochemical outcome of the Pd-catalyzed carbocyclization giving selectivity that has never before been observed. The directing group remains as a functional handle for subsequent constructive manipulations.

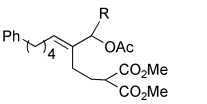
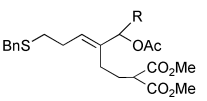
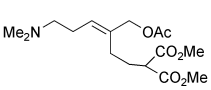


(2)

Table 1 summarizes the results of five-membered ring formation. Reaction of **2a** with sodium hydride in THF in the presence of palladium catalyst **1**, [(η^3-allyl)PdCl(PPh$_3$)], (10 mol%) at reflux for 18 h prompted cyclization to give the two isomeric cyclopentenes **3a** and **4a** as a > 9 : 1 mixture. With allylic acetate **2a** we did not expect to observe chelation of the palladium catalyst by the phenyl group and therefore anticipated regioselectivity of cyclization to be governed exclusively by steric factors. When a homoallylic sulfur moiety was tethered to allylic acetate **2b** the effect on the reaction was striking. The yield and rate of cyclization was dramatically increased (57% after only 1 h), and the change in regioselectivity was no less significant; a 2 : 3 ratio of **3b** and **4b** was isolated where addition

Table 1 Intramolecular directed allylation to form five-membered carbocycles



Substrate		Conditions	Time/h	Yield (%)	Ratio **3** : **4**
	**2a** R = Me	**a**[a]	18	46	> 9 : 1[b]
	**2b** R = H	**a**[a]	1	57	2 : 3
	2c R = Me	**a**[a]	0.3	62	1 : > 20
	2c R = Me	**b**[a]	2	58	1 : 9
	**2d**	**a**[a]	1	34	1 : > 20

[a] Conditions: **a.**1.2 equiv. NaH, 0.1 equiv. (η^3-allyl)PdCl(PPh$_3$) (**1**) THF, Δ **b.** 1.2 equiv. NaH, 0.1 equiv. (η^3-allyl)PdCl(PPh$_3$), **1**, THF, r.t. [b] 0.5 equiv of P(OPh)$_3$ added. Product ratios determined by ^{1}H NMR spectroscopy.

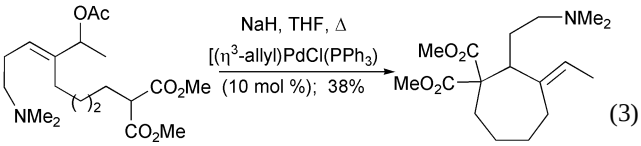
DOI: 10.1039/b302342g

proximal to the heteroatom was favored. The presence of a tertiary amine in **2d** imparted complete regiocontrol with reaction of the internal nucleophile proximal to the amine only.

The heteroatom is also apparently responsible for significant rate acceleration. Perhaps, through coordination to the palladium catalyst, it aids π-allyl complex formation by imparting pseudo-unimolecular kinetics. While the amine appeared superior to the thioether in imparting regioselectivity, we hoped that a π-allyl complex in which each allylic terminus was of comparable steric size would show improved selectivity when the thioether was present. Gratifyingly, a single regioisomer **4c** was now formed from the reaction of **2c**, favoring addition proximal to sulfur. That this reaction would also proceed at ambient temperatures is also noteworthy. Usually, higher temperatures are necessary to conduct such reactions.

We next investigated whether a similar trend would be observed during the formation of six membered carbocycles (Table 2). Control substrate **5a** reacted with the palladium catalyst **1** in THF in modest yield (66%). Carbocycle **6a** was the only product isolated, favoring attack at the least hindered allylic terminus. In contrast to the formation of the five-membered carbocycles, the introduction of a homoallylic thioether did not significantly alter this regioselectivity *i.e.* **5b**. However, it was remarkable that the presence of sulfur in the molecule was manifest by a dramatic increase in both rate and yield of reaction. Partially equalizing steric bulk on either side of the π-allyl complex gave the expected change in ratio of products. Introduction of a methyl group gave a result in which addition proximal to the sulfur heteroatom was favored for the first time (**5c**). A further increase in steric bulk by incorporating either an ethyl or a butyl group resulted in complete regiocontrol (**5d,5e**). Parallel to the results observed in the formation of five-membered carbocycles, the presence of a tertiary amine led to complete regioselectivity of cyclization (**5f**).

Seven-membered rings were also formed (eqn. 3) where the only product isolated resulted from substitution at the allyl terminus proximal to the heteroatom. No other cyclization products were isolated.

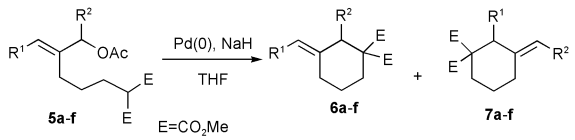


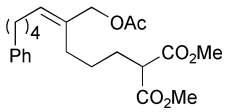
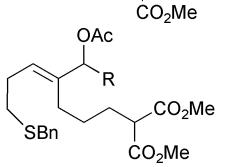
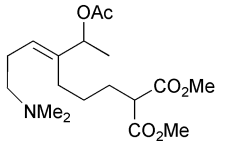
(3)

In summary, we have established that the regioselective cyclization of allylic acetates incorporating a tethered nucleophile to furnish five-, six- and seven-membered carbocycles is dominated by the presence of a homoallylic thioether or tertiary amine which provides a transient interaction between the substrate and reagent. These noteworthy examples represent the first ones where π-allyl palladium cyclizations are governed by use of a heteroatom as the reaction control element rather than by ring size or steric interactions. We have also demonstrated that heteroatoms capable of coordinating to palladium can, as well as reversing the expected regiochemical outcome, significantly alter reaction kinetics, thus facilitating formation of substances that would otherwise be inaccessible using such mild conditions. We have shown that nitrogen is superior to sulfur for imparting regioselectivity. Work is in progress to evaluate the scope of this reaction and to obtain more data on the superiority of nitrogen.

This work was supported by the National Science Foundation and the MDS Research Foundation.

Table 2 Intramolecular directed allylation to form six-membered carbocycles



Substrate		Conditions	Time/h	Yield (%)	Ratio **6** : **7**
	**5a**	**a**[a]	2	66	> 20 : 1
	**5b** R = H	**b**[a]	0.3	76	8 : 1
	5c R = Me	**b**[a]	8	46	3 : 7
	5d R = Et	**a**[a]	2	51	1 : > 10
	5e R = *n*Bu	**a**[a]	1.5	58	1 : > 20
	**5f**	**a**[a]	2[b]	53	1 : > 20

[a] Conditions: **a**. 1.2 equiv. NaH, 0.1 equiv. (η^3-allyl)PdCl(PPh_3) (**1**), THF, Δ; **b**. 1.2 equiv. NaH, 0.1 equiv. (η^3-allyl)PdCl(PPh_3), 1, THF, r.t.. [b] The reaction was probably completed sooner, however the product was copolar with S.M. so the reaction time was extended to ensure complete consumption of S.M. Product ratios determined by ^{1}H NMR spectroscopy.

Notes and references

1 For leading references, see: P. J. Harrington, in *Comprehensive Organometallic Chemistry II*, eds. E. W. Abel, F. G. A. Stone, G. Wilkinson, Pergamon, Oxford, 1995, **vol. 12**, ch. 8.2, p. 798; S. A. Godleski, in *Comprehensive Organic Synthesis*, eds. B. M. Trost, I. Fleming, M. F. Semmelhack, Pergamon, Oxford, 1991, **vol. 4**, ch. 3.3, pp. 585–661.

2 A. J. Blacker, M. J. Clarke, M. S. Loft and J. M. J. Williams, *Org. Lett.*, 1999, **1**, 1969.

3 E. Kienan and M. Sahai, *J. Chem. Soc., Chem. Commun.*, 1984, 648.

4 M. Moreno-Mañas and J. Rabas, *Tetrahedron Lett.*, 1989, **30**, 3109.

5 B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton and T. Dietsche, *J. Am. Chem. Soc.*, 1978, **100**, 3416.

6 J. P. Genet, M. Balabane, J. E. Backvall and J. E. Nystrom, *Tetrahedron Lett.*, 1983, **24**, 2745.

7 For example, see: J. Tsuji, H. Kataoka and Y. Kobayashi, *Tetrahedron Lett.*, 1981, **22**, 2575.

8 M. P. T. Sjogren, S. Hansson and B. Akermark, *Organometallics*, 1994, **13**, 1963; B. Akermark, K. Zetterberg, S. Hansson and B. Krakenberger, *J. Organomet. Chem.*, 1987, **335**, 133.

9 U. Leutenneger, G. Umbricht, C. Fahrni, P. V. Matt and A. Pfaltz, *Tetrahedron*, 1992, **48**, 2143; A. Pfaltz, *Acc. Chem. Res.*, 1993, **26**, 339; P. V. Matt, G. C. Lloyd-Jones, A. B. E. Minidis, A. Pfaltz, L. Macko, M. Neuberger, M. Zehnder, H. Ruegger and P. S. Pregosin, *Helv. Chim. Acta.*, 1995, **78**, 265.

10 M. E. Krafft, A. M. Wilson, Z. Fu, M. J. Procter and O. A. Dasse, *J. Org. Chem.*, 1998, **63**, 1748.

11 M. E. Krafft, M. Sugiura and K. A. Abboud, *J. Am. Chem. Soc.*, 2001, **123**, 9174.

12 K. Itami, T. Koike and J. Yoshida, *J. Am. Chem. Soc.*, 2001, **123**, 6957.

13 B. M. Trost, S. M. Mignani and T. N. Nanninga, *J. Am. Chem. Soc.*, 1988, **110**, 1602; B. M. Trost, *Angew. Chem., Int. Ed., Engl.*, 1986, **25**, 1.

14 *Typical experimental procedure*: To a solution of the allyl acetate (0.2 mmol) in THF (5 mL) at ambient temperature and under argon was added sodium hydride (0.24 mmol). After 2 min, catalyst **1** (10 mol%) was added and the mixture heated at reflux. When the reaction was complete (as indicated by TLC) the mixture was cooled, filtered through Celite, concentrated *in vacuo* and purified by flash column chromatography on silica gel. The regioisomers were not separable by flash chromatography.