Published in final edited form as:

J Am Chem Soc. 2006 May 10; 128(18): 6044–6045. doi:10.1021/ja0602501.

Palladium-Catalyzed Asymmetric Ring Expansion of Allenylcyclobutanols: An Asymmetric Wagner-Meerwein Shift

Barry M. Trost* and Jia Xie

Department of Chemistry, Stanford University, Stanford, California 94305-5080

In order to improve the efficiency of the synthesis of bioactive natural products, it is essential to develop new reactions in which bond formation has high atom economy, as well as chemo-, regio-, diastereo-, and enantioselectivity.¹ In this regard transition metal-catalyzed asymmetric allylic alkylation (AAA) is one of the most powerful tools.^{2,3} It has been shown that our family of ligands (Figure 1) can perform various palladium-catalyzed AAA reactions with excellent selectivity.⁴

Nevertheless, to generate the π -allylpalladium intermediate in allylic alkylation reactions, ionization of the leaving group is normally required. In order to enhance the simplicity and efficiency, a new method is required to initiate the reaction. Considering the hydrocarbonation of allenes catalyzed by palladium,^{5,6} our group has recently utilized the hydropalladation mechanism to generate the π -allylpalladium intermediate and achieve catalytic asymmetric addition of pronucleophiles to allenes,⁷ which fulfills the twin goals of high selectivity and atom economy.

We wondered whether the hydropalladation strategy could extend to intramolecular reactions, such that a catalytic asymmetric Wagner-Meerwein shift might be possible.⁸ Although a recent report showed that carbopalladation of allenyl-cyclobutanols could generate a π -allylpalladium intermediate which undergoes a Wagner-Meerwein shift, these reactions were not enantioselective.⁹ In this paper, we describe our efforts to effect asymmetric hydropalladation using palladium catalysts bearing our ligands that enable the catalytic asymmetric Wagner-Meerwein shift with allenylcyclobutanols initiated by hydropalladation (Scheme 1).

We chose benzyloxyallenylcyclobutanol **1** to begin the study. Without any additives, the ring expansion was very sluggish and gave low conversion. Both acidic conditions and higher temperatures accelerated the process. Interestingly, the combination of acid and base, for example benzoic acid and triethylamine gave the fastest reaction, which is consistent with our earlier results on the intermolecular nucleophilic addition of benzyloxyallene,⁷ in which control of pH is the key to good reactivity and selectivity.

With benzoic acid and triethylamine as the additives, the reaction was carried out with good yields and enantioselectivity at 60°C (Table 1). We further optimized the reaction conditions by varying ligand, solvent, additive, and temperature. The ee varied in different solvents (Table 1, entries 1–7). For **L1**, dichloro-ethane gave the best ee at 60 °C (Table 1, entry 7). Among our four ligands, **L3** gave the higher ee for the ring expansion of benzyloxyallenylcyclobutanol (Table 1, entries 7–10). Moreover, **L3** gave the highest reactivity in this ring expansion reaction. This result allowed us to lower the temperature to 30°C or r.t. (Table 1, entries 10–13), which resulted in a higher ee although a slight drop in yield. The decline in yield was caused by the hydrolysis of the alkoxyallene competing with ring expansion reactions at the lower

temperatures. By adding 4Å MS to prevent hydrolysis, we were able to improve the yield to 96% (Table 1, entry 14).

With the optimized reaction conditions, we examined the scope of the reaction by using different substrates (Table 2). The reaction tolerates a range of groups, including benzyl (Table 2, entry 1), 4-methoxybenzyl (Table 2, entry 2), simple alkyl (Table 2, entry 3), alkene (Table 2, entries 4 and 5), alkyne (Table 2, entry 6) and ester (Table 2, entry 10). It potentially provides various approaches to further functionalize, and thereby access, different synthetic targets. For instance, **8** and **10** can be used to synthesize chiral [4, 5] and [4, 6] spiro-ring systems, **21** and **22**, very simply by ring closing metathesis (**eq. 1**).

(1)

We have also studied 3,3-disubstituted cyclobutanols. However, their reactivity was poorer than the unsubstituted cyclobutanols and gave lower conversion at 30 °C. Reaction at elevated temperature (60°C) gave a full conversion with 10~20% decrease in ee using **L3**. Switching to ligand **L4**, which gives a higher ee at 60°C, solves this problem. This improvement is mainly due to **L4**'s rigid backbone, which makes its enantioselectivity more independent of the reaction temperature. As a result, we can perform the ring expansion of 3,3-disubstituted cyclobutanols at 60°C maintaining good ee (Table 2, entries 7~10).

This methodology is also amendable for 3-monosubstituted substrates, for example **24** (Scheme 2). Subjecting the major addition product **24a** to the ring expansion allows us to selectively generate two stereogenic centers of cyclopentanone **25** in one step.

The assignment of the absolute configuration was made by conversion to the diol **27** (Scheme 3), a known compound whose asymmetric synthesis depended upon a chiral auxiliary.¹⁰ This compound served as a useful intermediate to synthesize highly functionalized tetrahydrofuran natural products, for example *trans*-kumausyne.¹⁰ The stereochemistry of compound **4** could be rationalized by our proposed working model (Scheme 4).

In summary, we have developed a useful new method for the catalytic atom economic asymmetric Wagner-Meerwein shift of allenylcyclobutanols catalyzed by palladium, which provides a general way to synthesize cyclopentanones with α -chiral *O*-tertiary center. Moreover, the use of 3-monosubstituted substrate enables us to obtain excellent diastereoselectivity and enantio-selectivity. Studies of the mechanism and other substrates are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the National Science Foundation and National Institutes of Health for their generous support of our programs. Mass Spectra were provided by the Mass Spectrometry Regional Center of the University of California-San Francisco, supported by the NIH Division of Research Resources.

References

1. For review of atom economy see (a) Trost BM. *Science* 1991;254:1471. [PubMed: 1962206] (b) Trost BM. *Angew Chem, Int Ed Engl* 1995;34:259. (c) Trost BM. *Acc Chem Res* 2002;35:695. [PubMed: 12234199]
2. For transition-metal catalysis see (a) Noyori R, Kitamura M, Ohkuma T. *Proc Natl Acad Sci USA* 2004;101:5356. [PubMed: 15034179] (b) Trost BM. *Proc Natl Acad Sci USA* 2004;101:5348. [PubMed: 14990801] (c) Jacobsen EN, Pfaltz A, Yamamoto H. *Comprehensive Asymmetric Catalysis I–III*. Springer, Berlin, 2000.
3. For review (a) Trost BM, Van Vranken DL. *Chem Rev* 1996;96:395. [PubMed: 11848758] (b) Trost BM, Crawley ML. *Chem Rev* 2003;103:2921. [PubMed: 12914486]
4. For review see Trost BM. *Chem Pharm Bull* 2002;50(1):1. [PubMed: 11824567]
5. For reviews, see (a) Trost BM. *Chem Eur J* 1998;1:2405. (b) Yamamoto Y, Radhakishman U. *Chem Soc Rev* 1999;28:199. (c) Khan FA. *Chem Rev* 2000;700:3067. [PubMed: 11749314] (d) Ma S. *Chem Rev* 2005;705:2829. [PubMed: 16011326]
6. (a) Yamamoto Y, Al-Masum M, Asao N. *J Am Chem Soc* 1994;776:6019. (b) Yamamoto Y, Al-Masum M. *Synlett* 1995:969. (c) Yamamoto Y, Al-Masum M, Talkeda A. *Chem Commun* 1996:831. (d) Meguso M, Shin K, Yamamoto Y. *Tetrahedron Lett* 1996;37:7453. Trost BM, Jakel C, Plietker B. *J Am Chem Soc* 2003;125:4438. [PubMed: 12683811]
7. (a) Trost BM, Jäkel C, Plietker B. *J Am Chem Soc* 2003;125:4438. [PubMed: 12683811] (b) Trost BM, Simas ABC, Plietker B, Jäkel C, Xie J. *Chem Eur J* 2005;11:7075.
8. Trost BM, Yasukata T. *J Am Chem Soc* 2001;123:7162. [PubMed: 11459498] and references cited therein
9. Yoshida M, Sugimoto K, Ihara M. *Tetrahedron* 2002:7839. and references cited therein
10. (a) Brown MJ, Harrison T, Overman LE. *J Am Chem Soc* 1991;125:5365. (b) Brown MJ, Harrison T, Overman LE. *J Am Chem Soc* 1991;125:5378.

Figure 1.
Trost Ligands.

Scheme 1.
Rationale for Palladium-Catalyzed Ring Expansion

Scheme 2.

Diastereoselectivity of 3-Monosubstituted Cyclobutanol

Scheme 3.
Assignment of the Absolute Configuration

Scheme 4.
Mechanistic Rationale

Table 1

Optimization of Ring Expansion Reactions^a

entry	ligand	solvent	temp. (°C)	Yield (%) ^b	ee(%) ^c
1	L1	DMSO	60	41	64
2	L1	DMF	60	85	79
3	L1	CH ₃ CN	60	63	82
4	L1	Dioxane	60	40	80
5	L1	THF	60	90	80
6	L1	DME	60	89	81
7	L1	DCE	60	85	83
8	L2	DCE	60	33	57
9	L3	DCE	60	95	87
10	L4	DCE	60	86	84
11	L3	DCE	40	90	88
12	L3	DCE	30	75	92
13	L3	DCE	23	60	94
14 ^d	L3	DCE	30	96	92

^a Unless otherwise indicated, all reactions were performed using on a 0.2 mmol scale at 0.1 M for 2 to 24 h.

^b Isolated yield.

^c The ee values were determined by chiral HPLC.

^d Adding 4 Å MS

Table 2

Wagner-Meerwein Shift of Various Allenylcyclobutanols^a

Entry	substrate	product	yield ^d	ee ^e
1			96%	92%
2 ^b			97%	89%
3 ^b			100%	86% ^f
4 ^b			78%	87% ^f
5 ^b			100%	86% ^f
6 ^b			88%	84% ^f
7			95%	95%
8 ^c			92%	94%
9 ^c			93%	92%
10 ^c			80%	94%

^aUnless otherwise indicated, all reactions were performed on 0.5 mmol scale at 0.1 M for 12h at 23°C using **L3**^bPerformed at 30°C using **L3**.^cPerformed at 60°C using **L4**.

^d Isolated yield.

^e Unless otherwise indicated, ee values were determined by chiral HPLC.

^f Ee values were determined by chiral GC.