J|A|C|S
COMMUNICATIONS

Published on Web 03/25/2003

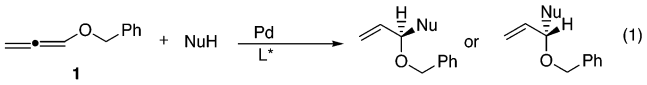
Palladium-Catalyzed Asymmetric Addition of Pronucleophiles to Allenes

Barry M. Trost,* Christoph Jäkel, and Bernd Plietker

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

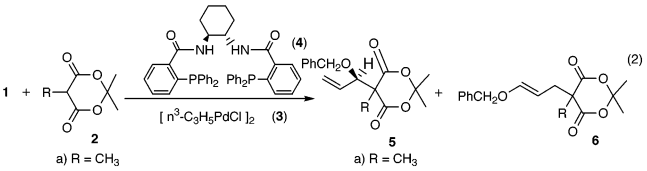
Received November 1, 2002; E-mail: bmtrost@stanford.edu

Performing complex synthesis by the use of simple addition reactions significantly enhances the efficiency of such strategies. Unfortunately, too few such reactions exist. One of the most important C−C bond forming processes is the alkylation of enolates. Such processes typically require a stoichiometric amount of base and use of electrophiles such as organohalides and pseudohalides. To enhance the utility of such processes, we engaged in the development of a hydrocarbonation of allenes catalyzed by palladium which meets the goal of an atom economic process because it is a simple addition where anything else is needed only catalytically.[2−4] The process would increase significantly in its power, if it can be performed asymmetrically. Scheme 1 outlines the envisioned catalytic cycle. With unsymmetrical allenes, the issue of regioselectivity as well as enantioselectivity also arises. Early work established that an oxygen substituent gave an electronic bias for nucleophilic addition to the substituted allene terminus in such additions.[3b] The value of oxygen substitution led us to focus on this substituent, that is, benzyloxyallene,[5] as shown in eq 1.[6]



(1)

Initial experiments were performed under basic conditions using methyl Meldrum's acid **2a** as the pronucleophile. Using 1 mol %



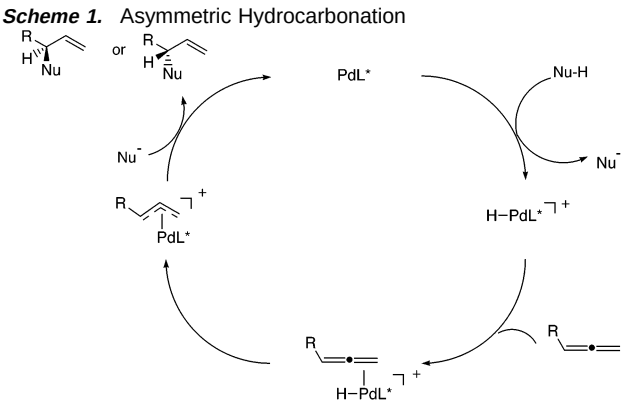
(2)

π-allylpalladium chloride dimer and 5 mol % ligand **4** in the presence of 5 mol % potassium *tert*-butoxide required elevated temperature (80 °C) in THF. Under these conditions, a 69% yield of a 3:1 ratio of branched (b, **5**) to linear (l, **6**) isomers was observed wherein the branched isomer showed a modest 38% ee. Addition of 4 mol % TBAB increased the regioselectivity to 7.3:1 and the ee to 72% (67% yield). Switching to DMSO where the reaction proceeded at 20 °C dramatically influenced both the regioselectivity (only **5**) and the ee (83%) wherein the product was isolated in 86% yield. Use of tetraalkylammonium chloride salts (tetrabutyl, tetrahexyl, and benzyltriethyl) showed similar results.

Using different batches of the Meldrum's acid led to irreproducibility of the results: the purer the Meldrum's acid, the lower the ee. Because malonic acid is a common contaminant, its effect on the reaction was pursued. Indeed, addition of up to 1 equiv of malonic acid fully restored reproducibility. Thus, the presence of base clearly is detrimental to the reaction, and optimization of the reaction as outlined in Scheme 1 should increase the concentration of the protonated palladium species.

In line with this suggestion, palladium trifluoroacetate was employed as the precatalyst with 1 mol % malonic acid and no

Scheme 1. Asymmetric Hydrocarbonation



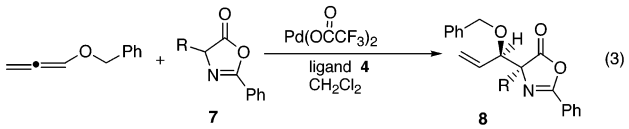
tetraalkylammonium salt as additive. Even in THF, the ee increased to 66%. A further increase to 85% ee occurred using methylene chloride. Replacing malonic acid by 1 mol % trifluoroacetic acid in methylene chloride gave the best result, an 81% yield with 94% ee. Additional trifluoroacetic acid decreased the rate of the reaction. Thus, the standard conditions became 1 mol % chiral catalyst in methylene chloride at ambient temperature. Table 1 and eq 2 summarize the results with various Meldrum acids and demonstrate the generality of the reaction.

Table 1. Asymmetric α-Alkoxyallylation of Meldrum Acids[a]

entry	**2** (R)	isolated yield **5**	ee[b]
1	CH_3 (a)	75% (a)	99%
2	$(CH_3)_2CHCH_2$ (b)	61% (b)	88%
3	$CH_2{=}CHCH_2$ (c)	82% (c)	96%
4	$PhCH_2$ (d)	90% (d)	91%
5	2-$C_4H_3OCH_2$ (e)	81% (e)	94%
6	HO (f)	63% (f)	82%

[a] All reactions were performed using a 1:1 ratio of alkene and Meldrum's acid, 1 mol % palladium trifluoroacetate, 1.25 mol % ligand **4**, and 1 mol % trifluoroacetic acid in methylene chloride (0.4 M) at room temperature. [b] Determined by chiral HPLC using a Daicel AD or OD column with 99:1 heptane:2-propanol as eluent.

The importance of quarternary amino acids led us to examine azlactones as suitable nucleophiles (eq 3). This class also raises the question of selectivity at the nucleophilic as well as electrophilic



(3)

center. Using the acidic conditions which worked so well for Meldrum's acids gave very poor conversions with azlactones. Using benzoic acid rather than trifluoracetic acid for the reaction of azlactone **7a** (R = CH_3) gave some conversion (25−35%) with a reasonable dr (>7:1) and ee of the major diastereomer (73−74%). The lower pK_a of azlactones as compared to that of Meldrum's

10.1021/ja029190z CCC: $25.00

acids accounts for this divergence in behavior. Indeed, use of 2 mol % potassium *tert*-butoxide provided complete conversion and isolation of the product in 80% yield with 7:1 dr and 73% ee.

From the Meldrum's acid results, it is clear that the reaction should be as acidic as possible. Thus, the reaction was buffered by using a carboxylic acid in conjunction with potassium *tert*-butoxide. Indeed, by adding 30 mol % benzoic acid, we obtained the alkylated azlactone **8a** (R = CH_3) with excellent selectivity, a 24:1 dr and 98% ee, while still maintaining reasonable conversion, 63% isolated yield. On the other hand, trifluoroacetic acid even at 2 mol % gave very low conversion. Hippuric acid (20 mol %) gave the best compromise whereby the alkylated product **8a** with a dr of 20:1 and ee of 93% was isolated in 85% yield. Using these buffered conditions, we allylated a range of azlactones as outlined in Table 2 and eq 3.[7]

Table 2. Asymmetric Alkoxyallylation of Azlactones[a]

entry	**7** (R)	isolated yield **8**	dr **8**[b]	ee **8**[b]
1	CH_3 (a)	85% (a)	20:1	93%
2	$(CH_3)_2CHCH_2$ (b)	83% (b)	20:1	94%
3	$CH_2{=}CHCH_2$ (c)	85% (c)	20:1	90%
4	$PhCH_2$ (d)	87% (d)	16:1	93%
5	$CH_3S(CH_2)_3$ (e)	67% (e)	13:1	85%

[a] All reactions were performed using a 1:1 ratio of allene and azlactone with 2 mol % palladium trifluoroacetate, 6 mol % ligand **4**, 2 mol % potassium *tert*-butoxide, and 20 mol % hippuric acid in methylene chloride (0.4 M) at room temperature. [b] Determined by chiral HPLC using a Daicel AD or OD column with 99:1 heptane:2-propanol.

Thus, a simple atom economical approach to allylic alkylations via a hydrocarbonation strategy can be performed with an alkoxyallene as the acceptor and Meldrum's acids or azlactones as the donors. The key for good reactivity and selectivity is control of pH to facilitate the hydropalladation. The required pH is a function of the pK_a of the pronucleophile. With a pronucleophile like Meldrum's acid whose pK_a is around 5,[8] a strong acid still allows sufficient concentration of the nucleophile (presumably the enol at the pH) to permit facile reaction. On the other hand, the azlactones whose pK_a is around 9[9] require somewhat more basic conditions for reasonable concentrations. Nevertheless, the strongest base is still only a potassium carboxylate. The fact that acids ranging from malonic (pK_a 2.8) to benzoic (pK_a 4.2) gave reasonable yields but hippuric (pK_a 3.6) proved best suggests that matching the acid to the nucleophile is important. The role of the pH of the reaction on the nature of the ligand should also be considered. The presence of secondary amides opens the prospect for deprotonation wherein the degree of deprotonation of the catalyst may impact its chiral recognition. Such ligand deprotonation does occur in our Mo-catalyzed asymmetric allylic alkylations using similar nucleophiles.[10] In asymmetric alkylations of ketone enolates with these palladium complexes, the use of excess strong base makes it highly probable that these secondary amides are deprotonated.[11] In the present case, it appears that such deprotonation is unfavorable. The excellent regio-, diastereo-, and enantioselectivity make this a valuable alternative to aldol type processes which fail with such stabilized nucleophiles due to the unfavorable equilibrium. Thus, the palladium-catalyzed asymmetric allylic alkylation embraces a new type of enantioselective C−C bond formation − addition of a C−H bond across an allene.

Acknowledgment. We thank the National Science Foundation and National Institutes of Health (GM 13598) for their generous support of our programs. Christoph Jäkel thanks the Alexander-von-Humboldt Foundation, and Bernd Plietker thanks the Deutscher Akademischer Austauschdienst for a postdoctoral fellowship that provided partial support. Mass spectra were provided by the Mass Spectrometry Facility, University of California − San Francisco, supported by the NIH Division Research Resources.

Supporting Information Available: Spectroscopic and analytical data for **5a**−**f** and **8a**−**e** and representative procedures for the synthesis of **5a** and **8a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Trost, B. M. *Science* **1991**, *254*, 1471.
(2) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156. Trost, B. M.; Michellys, P.-Y.; Gerusz, V. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1750.
(3) (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc* **1994**, *116*, 6019. (b) Yamamoto, Y.; Al-Masum, M. *Synlett* **1995**, 969. (c) Yamamoto, Y.; Al-Masum, M.; Takeda, A. *Chem. Commun.* **1996**, 831. (d) Meguro, M.; Shin, K.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 7453.
(4) For reviews, see: Trost, B. M. *Chem.-Eur. J.* **1998**, *1*, 2405. Yamamoto, Y.; Radhakrishman, U. *Chem. Soc. Rev.* **1999**, *28*, 199. Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067.
(5) Brandsma, L.; Nerkruijsse, H. D. Synthesis of Acetylenes, Allenes and Cumulenes. *Studies in Organic Chemistry 8*; Elsevier: Armsterdam, New York, 1981.
(6) For Pd-catalyzed asymmetric hydroamination of 1,3-dienes, see: Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366. For asymmetric carboannulation involving allenes, see: Zenner, J. M.; Larock, R. C. *J. Org. Chem.* **1999**, *64*, 7312.
(7) New compounds have been fully characterized spectroscopically, and elemental composition has been established by high-resolution mass spectrometry or combustion analysis.
(8) Eistert, B.; Geiss, F. *Tetrahedron* **1959**, *7*, 1.
(9) Goodman, M.; Levine, L. *J. Am. Chem. Soc.* **1964**, *86*, 2918.
(10) Krska, S. W.; Hughes, D. L.; Reamer, R. A.; Mathre, D. J.; Sun, Y.; Trost, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12656. Trost, B. M.; Dogra, K.; Hachiya, I.; Emura, T.; Hughes, D. L.; Krska, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1929.
(11) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. Trost, B. M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3492.

JA029190Z