Asymmetric Arylation of Ketone Enolates

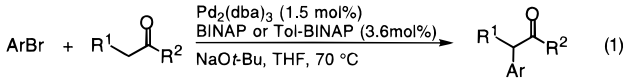
Jens Åhman, John P. Wolfe, Malisa V. Troutman, Michael Palucki,† and Stephen L. Buchwald*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Received November 4, 1997

The creation of all-carbon quaternary centers with absolute control of stereochemistry remains a great challenge in organic synthesis.[1] A number of methods have been developed to accomplish this task, including the Pd-catalyzed asymmetric allylations of soft enolates reported by Hayashi (β-diketones)[2] and Trost (β-ketoesters).[3] We now report the first examples, to our knowledge, of the catalytic asymmetric arylation of ketone enolates to produce all-carbon quaternary centers.[4]

We recently disclosed that nascent ketone enolates generated in the presence of an aryl bromide and a catalytic quantity of a Pd catalyst are converted to their α-aryl derivatives with a high degree of regioselectivity (eq 1).[5−7] As our initial protocol

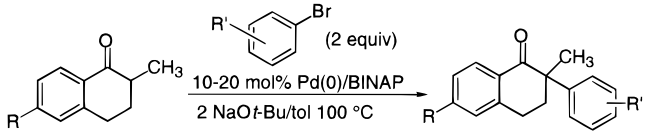


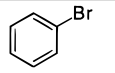
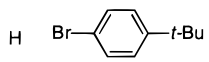
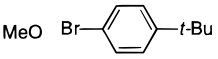
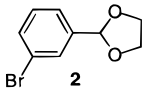
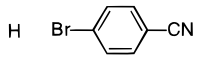
(1)

employed (*S*)-Tol-BINAP/$Pd_2(dba)_3$ [dba= dibenzylideneacetone] as catalyst, the application of this methodology to asymmetric arylation processes was of interest. Our initial attempts at asymmetric arylation to produce tertiary stereocenters either by direct arylation or desymmetrization of cyclic ketones gave disappointing results. Our attention then turned to the formation of quaternary centers. In our first experiments, we were able to asymmetrically arylate 2-methyl-α-tetralone with 1-bromo-4-*tert*-butylbenzene to give the desired product with an enantiomeric excess (ee) of 61%, albeit in low yield. Subsequent experimentation has led to an improvement upon these initial results, which we now report.

We found that both the yield and the enantioselectivity of the arylation of 2-methyl-α-tetralone could be brought to good levels by running the arylation using 10−20 mol % Pd(0)/12−24 mol % BINAP in toluene at 100 °C.[8,9] It was found that an excess of aryl bromide was necessary to ensure complete conversion of the ketone; 2-methyl-1-naphthol, biaryls, and compounds resulting from aldol condensation were formed as side products. In some reactions, the α-phenylated ketone was also observed as a side product. Subsequent experiments demonstrated that the latter side product was a result of aryl transfer from the phosphine ligand.[10] Using the conditions described above, the arylations of 2-methyl-α-tetralone proceeded with enantioselectivities up to 88% (Table 1).[11] We have also briefly examined the reactions of 2-methyl-1-indanone, **1**. Using 5 mol % $Pd(OAc)_2$/12 mol % BINAP, the reaction with bromide **2** proceeded smoothly to give **3** in 79% yield with an ee of 70% (eq 2).[12] Surprisingly, preliminary attempts to couple para-substituted aryl bromides with **1** gave products which were racemic.

Table 1



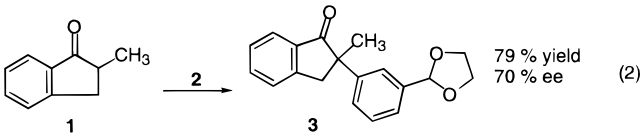
R	R'	% ee	% yield
H		73	66
H		88	73[a]
MeO		77	56[b]
H	 **2**	84	74
H		61	40[c]

[a] Product contains 4% of 2-methyl-2-phenyl-1-tetralone and 3% of a regioisomer which was present in the starting aryl bromide (percentages determined by GC analysis). [b] Product contains 3% of a regioisomer which was present in the starting aryl bromide (percentages determined by GC analysis). [c] The reaction was run at 70 °C using 5.0 equiv of halide and 5.0 equiv of NaO*t*Bu.

† Current address: Merck & CO., Inc., P.O. Box 2000, RY55-228, Rahway, NJ, 07605-0900.

(1) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.
(2) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113−120.
(3) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879−7880.
(4) The Pd-catalyzed asymmetric arylation of a silyl ketene acetal, [E-MeCH=C(OMe)($OSiMe_3$)], using a stoichiometric amount of TlOAc to form tertiary carbon centers has been reported (ee's range from 37 to 54%; only two aryl halides were examined). The asymmetric arylation of the corresponding tin enolate was also studied, although lower ee's were obtained: Galarini, R.; Musco, A.; Pontellini, R.; Santi, R. *J. Mol. Cat.* **1992**, *72*, L11−L13.
(5) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109.
(6) (a) Similar processes (as in ref 5a) have recently been described by others: Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382−12383. Muratake has recently reported a related Pd-catalyzed intramolecular α-arylation of ketones: (b) Muratake, H.; Hayakawa, A.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7577−7580. (c) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581−7582. (d) Satoh has recently reported a single example of the Pd-catalyzed diarylation of 1,3-diphenylacetone with iodobenzene to form 1,1,3,3-tetraphenylacetone: Satoh, A.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740−1742.
(7) For other examples of enolate α-arylation, see references contained in refs 5 and 6c.
(8) Control experiments were run with no palladium catalyst in the presence of NaHMDS at 100 °C for the reaction of 2-methyl-1-tetralone with 1-bromo-4-*tert*-butylbenzene and with 4-bromobenzonitrile. 1-Bromo-4-*tert*-butylbenzene did not react with the tetralone in the absence of palladium catalyst. The reaction involving 4-bromobenzonitrile showed ∼7% conversion after 1 h, but did not proceed further after another 2 h of heating.
(9) Reactions of 2-ethyl-1-tetralone are inefficient under these conditions.
(10) Using Tol-BINAP instead of BINAP gave small amounts of the α-(*p*-tolyl) ketone, and none of the phenylated ketone could be detected.
(11) Representative procedure: An oven-dried Schlenk tube was charged with $Pd_2(dba)_3$ or $Pd(OAc)_2$ (10−20 mol % Pd), (S)−(−)-BINAP (12−24 mol %, 1.2 L/Pd), and sodium *tert*-butoxide (96 mg, 1.0 mmol). The tube was purged with argon, and toluene (6 mL) was added. The mixture was stirred at room temperature for 1 min. The aryl halide (1.0 mmol) and an internal standard (dodecane, 0.115 mL, 0.5 mmol) were added, and the mixture was stirred at room temperature for 1 min. 2-Methyl-1-tetralone (0.075 mL, 0.5 mmol) and additional toluene (3 mL) were added, and the reaction mixture was heated to 100 °C with stirring until the ketone had been consumed as judged by GC or TLC analysis. The reaction mixture was cooled to room temperature, the reaction was quenched with saturated aqueous ammonium chloride (∼5 mL), and the solution was diluted with ether (∼10 mL). The layers were separated, the aqueous portion was extracted with ether (∼20 mL), and the combined organic layers were washed with saturated brine (∼10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel. Products which were difficult to completely separate from BINAP by silica gel chromatography were purified according to an alternative workup procedure. See the Supporting Information for full experimental details.

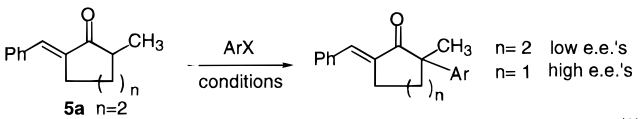
S0002-7863(97)03794-3 CCC: $15.00
Published on Web 02/12/1998



(2)

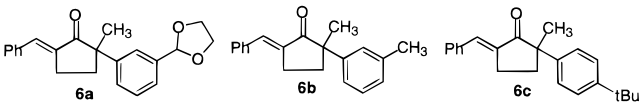
We next extended our investigation to include some α′-blocked α-methylcycloalkanones. These studies gave some enigmatic yet intriguing results.

For example, treatment of 2-methylcyclohexanone derivative **5a**[13] with a number of aryl bromides under conditions similar to those described above (or using NaHMDS[14] as base) yielded products with very low ee's (eq 3). However, the reactions of



(3)

the analogue **5b**[15] proceeded with high yields and with extremely



86 % yield, 95 % ee (NaHMDS, 10 mol% $Pd_2(dba)_3$/BINAP)

80 % yield, 94 % ee (NaO*t*Bu, 20 mol% $Pd(OAc)_2$/BINAP)

75 % yield, 98 % ee (NaO*t*Bu, 20 mol% $Pd(OAc)_2$/BINAP)

Figure 1.

high levels of enantioselecitivity as is shown above (Figure 1). Meta- or para-substituted aryl bromides, coupled with **5b** to give the desired products in very good yield and in a highly enantioselective fashion. If NaHMDS and $Pd_2(dba)_3$ were used in place of NaO*t*-Bu and $Pd(OAc)_2$, **6c**[16] was formed in 91% yield and with an ee of 92%.

There are a number of mysterious features of these reactions. For example, we currently have no good explanation for the difference in levels of enantioselectivity observed for the reactions of **5a** and **5b** under identical reaction conditions. Moreover, while the reactions of **5b**, shown above, proceed with high levels of enantioselectivity, in preliminary studies, similar reactions with 2-bromopropene, 2,4-dimethylbromobenzene, or the triflate derived from 4-hydroxy(methyl benzoate) yielded racemic products.

The mechanism of this reaction presumably follows a similar pathway to the one postulated for the nonasymmetric Pd-catalyzed α-arylation of ketones.[5] At this point in time, it is not clear which step, or steps, in the catalytic cycle determine the enantioselectivity of the overall process.

In summary, we have described the first examples of the catalytic asymmetric arylation of ketone enolates. These processes, in some instances, proceed in good yield and with very high levels of enantioselectivity. Our future work will be devoted to trying to understand the nuances of these processes in order to rationalize and generalize these transformations.

Acknowledgment. We thank the National Institutes of Health and the National Cancer Institute (Training Grant NCI no. CI T32CA09112) for their generous support of this work. We gratefully acknowledge additional unrestricted support from Pfizer, Merck, and Novartis. M.P. thanks the NIH for a postdoctoral fellowship. J.P.W. is a recipient of fellowships from the Organic Division of the American Chemical Society sponsored by Schering-Plough and from Boehringer-Ingelheim for which he is thankful. J.Å. is a Wallenberg Foundation Postdoctoral Fellow.

Supporting Information Available: Complete experimental procedures and characterization data for all new compounds (8 pages). See any current masthead page for ordering information and Web access instructions.

JA973794Z

(12) In preliminary experiments we have shown that **1** reacts with 2-bromopropene to give product with an ee of ∼60−70%. It is worth noting that an asymmetric vinylation/olefin hydrogenation sequence is the synthetic equivalent of a catalytic asymmetric alkylation.

(13) Johnson, W. S. *J. Am. Chem. Soc.* **1943**, *65*, 1317−1324.

(14) NaHMDS = sodium hexamethyldisilazide (sodium bis(trimethylsilyl)-amide).

(15) Sato, T.; Hayase, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3384−3389.

(16) This product contained 2% (as judged by GC analysis) of a regioisomer which was also present in the starting aryl halide. No regioisomers were observed with any of the other compounds reported in this paper which were made from halides other than 1-bromo-4-*tert*-butylbenzene.