J|A|C|S
COMMUNICATIONS

Published on Web 02/27/2003

A New Highly Asymmetric Chelation-Controlled Heck Arylation

Peter Nilsson, Mats Larhed, and Anders Hallberg*

Department of Organic Pharmaceutical Chemistry, Uppsala Biomedical Centre, Uppsala University, P.O. Box 574, SE-751 23 Uppsala, Sweden

Received December 9, 2002; E-mail: anders.hallberg@farmkemi.uu.se

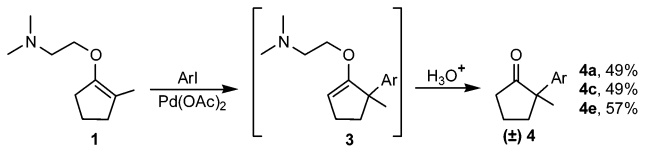
The interest in effective and robust methods that generate carbon−aryl bonds in the α-position to a ketone has increased since the discovery of the Pd(0)-catalyzed arylation of ketone enolates.[1] Recently, this direct methodology was further developed to allow formation of 2-aryl-2-methyl cycloalkanone derivatives with good to excellent enantioselectivities.[2] In 2001, we reported on the use of a coordinating auxiliary to facilitate the synthesis of 2,2-diarylated acetaldehydes[3] via a palladium-catalyzed Heck coupling procedure.[4] Because this chelation-accelerated Heck protocol[5] proved to be both selective and effective in generating highly substituted double bonds, we decided to explore the arylation of the tetra-substituted and two-carbon oxygen−nitrogen tethered enol ether **1** (Scheme 1). The couplings of **1** were performed with 2-iodoanisole **2a**, 2-iodotoluene **2c**, and 3-iodoanisole **2e** as arylating agents and potassium carbonate as the base. After reaction times of 42−72 h followed by rapid hydrolyses of **3**, the compounds **4a**, **c**, and **e** were obtained in good two-step yields. In contrast to the direct coupling to the enolate of the cyclic ketone, the Heck arylation of the corresponding **1** requires neither a strong base nor a blocking of the α-methylene carbon.

These initial examples demonstrated that the highly substituted enol ether **1** is reactive under the standard Heck conditions employed. This outcome is probably attributed to a chelation-accelerated and regioselective insertion, after coordination of the oxidative addition complex to the amino group (**A**, Scheme 2) and subsequent π-complex formation (**B**).

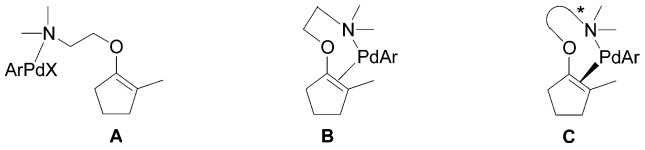
Considering that olefin **1** contains a prochiral double bond, the obvious question arose whether a chiral tertiary amino group could direct the oxidative addition complex exclusively from a selected face (π-complex **C**) and thus control the diastereotopicity of the insertion. To the best of our knowledge, there is only one previous report on an asymmetrical, intermolecular Heck reaction relying on chelation-control.[6] The inexpensive and commercially available amino alcohol (*S*)-1-methyl-2-pyrrolidine-methanol was selected as a suitable chiral metal-coordinating auxiliary[7] for stereoselective Heck arylations. The prolinol vinyl ether **6a** was prepared, via an acid-catalyzed acetalization-elimination protocol, from **5** (Scheme 3), similar to the method used for the preparation of the achiral **1**. The substrate for the arylation reaction (**6a**) was smoothly separated from the regioisomeric product (**6b**) by silica chromatography.

Pure **6a** (1.3 equiv) was arylated with nine different aryl halides (**2a**−**i**) (0.60 mmol scale, 1 equiv). A phosphine-free catalytic palladium system (3% Pd) was utilized to minimize interference from metal coordinating ligands.[8] Operationally, all components were added to aqueous DMF, and the vessel was sealed under air and heated for 18−68 h. Most rewardingly, the presenting power of the tertiary amino group in **6a** proved to be sufficiently effective for a regio- and stereoselective α-arylation to occur (Scheme 4). After the syn β-hydrogen elimination generating **7a**−**g**, a convenient acid mediated hydrolysis provided enantiomerically enriched cyclopentanones **4a**−**g** (90−98% ee). Notably, the quaternary chiral center was created with excellent enantioselectivity.[9] The preparative

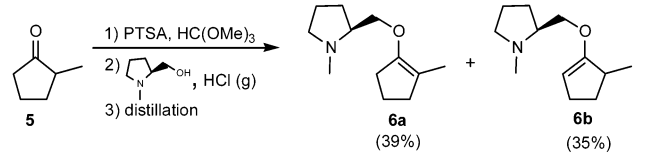
Scheme 1



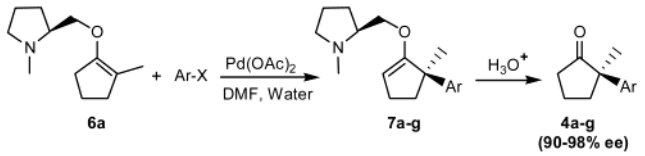
Scheme 2



Scheme 3



Scheme 4



results are presented in Table 1. Full conversions of the arylating agents were achieved in all cases, and the nonoptimized yields in the two-step sequence varied from 45 to 78%.

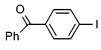
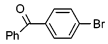
As is evident from Table 1, there was no obvious structure/enantioselectivity relationship (cf. entries 1 and 8), although both of the large 1-naphthyl halides **2f** and **2g** furnished lower yields and enantioselectivities (entries 6 and 7). In contrast, sterically demanding ortho-substituted **2a** and **2c** (entries 1 and 3) produced optical purities similar to those of the nonhindered isomers **2b** and **2e** (entries 2 and 5). In fact, entry 1 represents the highest reported stereoselectivity obtained in an asymmetric Heck arylation where a kinetic resolution process was not involved.

Although no mechanistic studies have been conducted, an involvement of a *N*-chelated π-intermediate similar to **D** (Chart 1)[10] might account for the excellent regio- and stereochemical outcome of the arylation.[11]

The major diastereomer of **7** is likely to be formed through Si-face insertion via the intermediate **D**.[12] The complex **D** is expected to adopt a gauche conformation relative to the O−C═C plane to avoid steric interactions between the methylene group attached to the oxygen atom and the methyl group on the double bond.[13] Upon Pd-coordination, the nitrogen becomes chiral, and the metal will thus coordinate the amine in a cisoid fashion relative to the hydrogen at the neighboring chiral carbon. After insertion, the nitrogen can

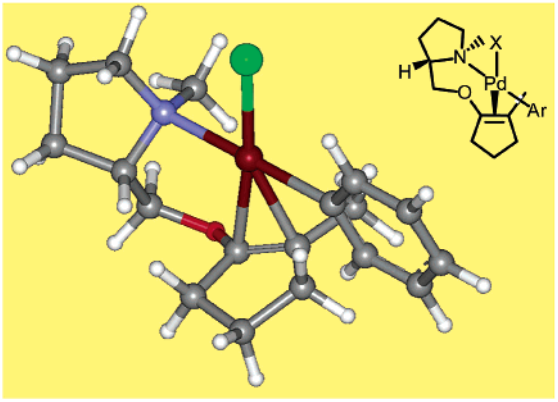
10.1021/ja029646c CCC: $25.00

Table 1. Chelation-Controlled Asymmetric Arylation of **6a** with Aryl Halides

Entry	Aryl Halide		Temperature	Time	Isolated Yield[a]	ee[b]	$[\alpha]_D^{23}$
1		**2a**	70 °C	24 h	67(%) **4a**	98(%)	+39°
2		**2b**	70 °C	18 h	54(%) **4b**	93(%)	+88°
3		**2c**	80 °C	30 h	50(%) **4c**	94(%)	+60°
4		**2d**	70 °C	68 h	61(%) **4d**	94(%)	+54°
5		**2e**	70 °C	18 h	68(%) **4e**	93(%)	+88°
6		**2f**	80 °C	48 h	45(%) **4f**	90(%)	+77°
7		**2g**	100 °C	48 h	49(%) **4f**	91(%)	+80°
8		**2h**	80 °C	24 h	47(%)[c] **4g**	97(%)	+48°
9		**2i**	100 °C	24 h	78(%) **4g**	94(%)	+45°

[a] Cumulative two-step yield after silica column chromatography (>95% purity by GC-MS). [b] Ee of (+) isomer of **4** as determined by chiral HPLC or chiral GC. [c] Yield calculated after intermediate isolation of **7g** (53%) and subsequent hydrolysis (88%).

Chart 1. Proposed Structure of Chelated π-Intermediate **D**



participate in the generation of the six-membered palladacycle prior to the subsequent β-elimination. The presentation of the oxidative addition complex via nitrogen coordination explains the high reactivity of the system[14] and why the quaternary center can be created. To investigate the difference in reaction rate enhancement, a competitive experiment[3,15] with **1** (0.5 equiv) and **6a** (0.5 equiv) and phenyl iodide (4 equiv) was performed at 50 °C. A ^{1}H NMR analysis after 45 h proved that nearly equal amounts of phenylated **3d** and **7d** had been formed. This result suggests that the accelerating capacities of the dimethylamino- and the *N*-methylated pyrrolidin frameworks are comparable.

In conclusion, the described chelation-controlled Heck methodology provides an alternative and mild approach to 2-aryl-2-methylcyclopentanones that delivers good to very good two-step yields. The reactions were performed under air with a weak base, and the enantioselectivities of the produced cyclopentanones are the highest reported so far. An extension to other cyclic ketones and new classes of chelating substrates seems promising.

Acknowledgment. We thank the Swedish Foundation for Strategic Research, the Swedish Research Council, and Dr. Boris Schmidt and Dr. Wilfried A. König for help with the chiral GC.

Supporting Information Available: Experimental procedures, and spectroscopic and analytical data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Hamada, T.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 999−1001. (b) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996−8002. (c) Fox, J. M.; Huang, X. H.; Chieffi, A.; Buchwald, S. L. *J.* Am. Chem. Soc. **2000**, *122*, 1360−1370. (d) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382−12383. (e) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109.

(2) (a) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261−1268. (b) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918−1919.

(3) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217−8225.

(4) (a) Heck, R. F. *Org. React.* **1982**, *27*, 345−363. (b) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371−7395. (c) Larhed, M.; Hallberg, A. In *Handbook of Organo-Palladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, pp 1133−1178. (d) Shibasaki, M.; Miyazaki, F. In *Handbook of Organo-Palladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, pp 1283−1315.

(5) For examples of related chelation-controlled Heck reactions, see: (a) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577−11585. (b) Badone, D.; Guzzi, U. *Tetrahedron Lett.* **1993**, *34*, 3603−3606. (c) Larhed, M.; Andersson, C. M.; Hallberg, A. *Acta Chem. Scand.* **1993**, *47*, 212−217. (d) Andersson, C. M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757−5761.

(6) Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129−7130.

(7) For examples of metal chelating chiral auxiliary in non-Heck transformations, see: (a) Westwell, A. D.; Williams, J. M. J. *Tetrahedron* **1997**, *53*, 13063−13078. (b) Breit, B. *Chem.-Eur. J.* **2000**, *6*, 1519−1524.

(8) General experimental procedure: Olefin **6a** (0.78 mmol), aryl halide **2a**−**i** (0.60 mmol), LiCl (1.2 mmol), NaOAc (0.72 mmol), K_2CO_3 (0.72 mmol), $Pd(OAc)_2$ (0.018 mmol), and H_2O (0.2 mL) were mixed in 2 mL of DMF and heated at a given time and temperature (Table 1).

(9) Reviews covering the creation of chiral quaternary centers: (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401.

(10) The proposed structure of the π-intermediate **D** was obtained by semimanual modeling, see Supporting Information.

(11) (a) Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505−2079. (b) McCrindle, R.; Ferguson, G.; Khan, M. A.; McAlees, A. J.; Ruhl, B. L. *J. Chem. Soc., Dalton Trans.* **1981**, 986−991. (c) Thorn, D. L.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 2079−2090.

(12) For a discussion regarding the diastereoselectivity, see Supporting Information.

(13) For ^{17}O NMR and conformation of cyclic vinyl ethers, see: (a) Taskinen, E.; Ora, M. *Magn. Reson. Chem.* **1995**, *33*, 239−243. (b) Taskinen, E.; Hellman, J. *Magn. Reson. Chem.* **1994**, *32*, 353−357.

(14) We have previously shown that chelating tertiary amine tethered vinyl ethers are more reactive than the noncoordinating alkyl counterparts in Heck arylations (see refs 3 and 5c,d).

(15) Westwell, A. D.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1−2.

JA029646C