ORGANIC LETTERS

2009
Vol. 11, No. 7
1543−1546

Diastereoselective Room-Temperature Pd-Catalyzed α-Arylation and Vinylation of Arylmandelic Acid Derivatives

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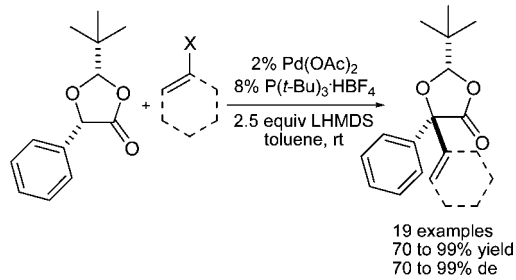
Received January 21, 2009

ABSTRACT



Palladium-catalyzed α-arylation and vinylation of dioxolane (*S,S*)-I, easily obtained from (*S*)-mandelic acid, proceeds with high yields and excellent diastereoselectivity at room temperature employing commercially available P(*t*-Bu)$_3$·HBF$_4$ and Pd(OAc)$_2$ as a catalytic precursor system. This method displays general utility for a large variety of aryl, heteroaryl, and vinyl bromides.

Fully substituted carbon centers are found in a variety of natural products and other molecules with pharmacological and medicinal applications. Accordingly, methods able to construct these sterically hindered positions selectively are highly valuable.[1] Among the existent protocols, metal-catalyzed α-arylations and α-vinylations[2,3] are powerful, established methods for accessing stereogenic centers.[3a,4] In line with our desire to obtain target compounds with high potential for pharmacological application, we decided to develop the α-arylation of mandelic acid derivatives. Mandelic acid is a ubiquitous biological intermediate with antibacterial properties.[5] Certain derivatives show muscarinic antagonist properties.[6] Recently, enantiomerically enriched

(1) Selected examples in enantioselective construction of quaternary centers: (a) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. A. *Eur. J. Org. Chem.* **2007**, 5969. (b) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (d) Dessinova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (e) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (f) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley & Sons: New York, 2000; Chapter 8E. (g) Donde, Y.; Overman, L. E. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley & Sons: New York, 2000; Chapter 8G.

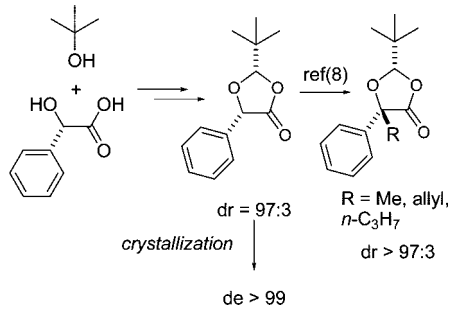
(2) Selected reviews in α-arylation of carbonyl compounds: (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (b) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211.

(3) Selected references on α-arylation of ketones: (a) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (c) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (d) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209. (e) Marion, N.; Navarro, O.; Kelly, R. A., III.; Nolan, S. P. *Synthesis* **2003**, 2590. Selected references on α-arylation of esters: (f) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996. (g) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1549. (h) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1545. Selected references on α-arylation of amino acid derivatives: (i) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465. (j) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410. Selected references on α-arylation of amides: (k) Cossy, J.; de Filippis, A.; Pardo, D. G. *Org. Lett.* **2003**, *5*, 3037. (l) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976. Selected references on α- vinylation of ketones: (m) Hamada, T.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 999. α-Arylation of aldehydes: (n) Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101. (o) Lavallo, V.; Canac, Y.; Prasang, C.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705. (p) Martin, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236. (q) Vo, G. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2127. (r) Martin, R.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 4561.

10.1021/ol900131q CCC: $40.75
Published on Web 03/02/2009

mandelic acid has been obtained via α-arylation using Ley's auxiliary.[7] The dioxolane (*S*,*S*)-**I**[8] derivative of mandelic acid has been used as a substrate in alkylations[9] and Pd-catalyzed allylic substitutions[10] and as a chiral auxiliary for the synthesis of α-hydroxy acids,[11] diols,[12] *C*-glycosyl norstatines,[13] and nitrobenzophenones.[14] The principle behind the selectivity in the majority of these processes is the self-regeneration of the stereocenter at the α-carbon (Scheme 1).[15]

Scheme 1. Synthesis of Dioxolane Derivatives



To the best of our knowledge, no Pd-catalyzed asymmetric arylation or vinylation has been previously reported using (*S*,*S*)-**I**.

Herein, we describe a highly efficient and general approach for the α-arylation and -vinylation of mandelic acid derivative using a chiral rigid five-membered ring to control the stereochemical pathway of the process. After cleavage of the auxiliary, the resulting compounds contain fully substituted centers and are easily converted to the corresponding α-hydroxy acids and 1,2-diols in high optical purity.[16]

Several bases, solvents, and palladium sources were tested in the arylation of dioxolane (*S*,*S*)-**I**[17] with 4-*tert*-butylbromobenzene (Figure 1). The most favorable conditions were

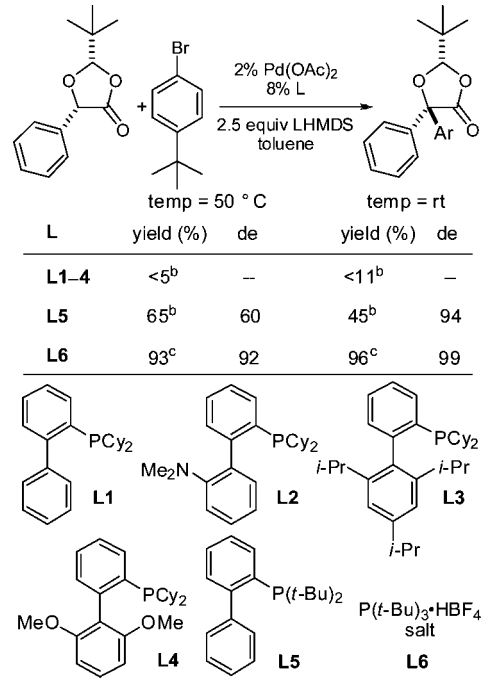


Figure 1. Pd-catalyzed α-arylation of (*S*,*S*)-**I** using **L1**−**L6**. (a) Reaction conditions: 2.3 mmol of dioxolane **I**, 1 mmol of ArBr, 2 mol % of $Pd(OAc)_2$, 8 mol % of **L1**−**L6**, 2.5 mmol of LHMDS in toluene (1 mL/0.25 mmol of ArBr). Diastereomeric ratio determined by HPLC. No coupling products were formed in the absence of catalyst. (b) Determined by GC. (c) Percent isolated yield.

found using $Pd(OAc)_2$ as the metal source and LHMDS as the base at 50 °C in toluene for 12 h. An excess of dioxolane (2.3 equiv) was necessary to achieve full conversion of the aryl halide due to the formation of Claisen byproducts from **I** and its enolate.

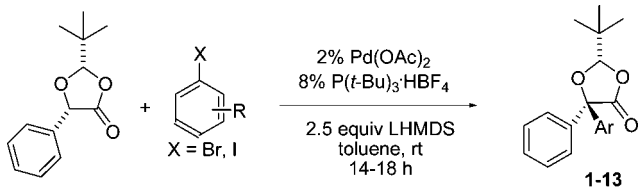
Among the ligands examined, air-stable P(*t*-Bu)$_3$•HBF$_4$ (a ligand that has been used in the α-arylation of esters[3g,h]) gave the best results, yielding the desired product in 93% yield and 96:4 diastereomeric ratio (dr).

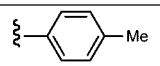
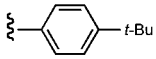
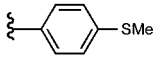
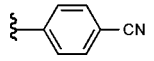
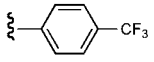
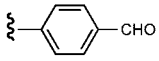
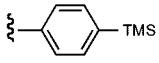
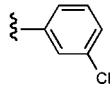
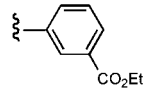
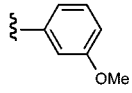
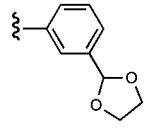
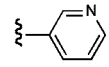
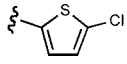
Remarkably, this catalytic system was also effective at *room temperature*, maintaining the activity and increasing the diastereomeric excess (de) from 92% to 99%.[3f]

Encouraged by these preliminary results, we decided to explore the generality of this transformation. As shown in Table 1, we were pleased to find that *both* electron-donating and electron-withdrawing substituents are well accommodated independently of their position (*para* or *meta*) in

(4) (a) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (b) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500. (c) Chietti, A. K.; Ahman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897. (d) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402.
(5) Hamilton-Miller, J. B.; Brumfitt, J. W. *Invest. Urol.* **1977**, *14*, 287.
(6) (a) Kiesewetter, D. O.; Silverton, J. V.; Eckelman, W. C. *J. Med. Chem.* **1995**, *38*, 1711. (b) Kiesewetter, D. O.; Carson, R. E.; Jagoda, E. M.; Endres, C. J.; Der, M. G.; Herscovich, P.; Eckelman, W. C. *Bioorg. Med. Chem.* **1997**, *5*, 1555.
(7) Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182.
(8) Grover, P. T.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem.* **2000**, *65*, 6283.
(9) Frater, G.; Müller, U.; Günther, W. *Tetrahedron Lett.* **1981**, *42*, 4221.
(10) Moorlag, H.; De Vries, J. G.; Kaptein, B.; Schoemaker, H. E.; Kamphuis, J.; Kellogg, R. M. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 129.
(11) (a) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704. (b) Barroso, S.; Blay, G.; Cardona, L.; Ferndandez, I.; Garcia, B.; Pedro, J. R. *J. Org. Chem.* **2004**, *69*, 6821.
(12) (a) Hof, P. R.; Kellogg, R. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2051–2060. (b) Scholtis, S.; Ide, A.; Mahrwald, R. *Org. Lett.* **2006**, *8*, 5353.
(13) Guerrini, A.; Varchi, G.; Battaglia, A. *J. Org. Chem.* **2006**, *71*, 6785.
(14) Blay, G.; Cordona, L.; Fernandez, I.; Michelena, R.; Pedro, J. R.; Ramirez, T.; Ruiz-Garcia, R. *Synlett* **2003**, 2325.
(15) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708.
(16) α-hydroxy acids: (a) Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids in Enantioselective Synthesis*; VCH: Weinheim, 1997. Diols: (b) Zaitsev, A. B.; Adolfssom, H. *Synthesis* **2006**, 1725. (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(17) The synthesis of (*S*,*S*)-**I** is reproductible. See ref 7.
(18) Using chiral auxiliaries: see ref 6. Examples of asymmetric intramolecular α-arylation: (a) Fortanet, J.-G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 8108. (b) Jia, X.-Y.; Hillgren, J. M.; Watson, L. E.; Marsden, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, 4040. For examples of nonasymmetric α-arylations: see ref 3j and: (d) Liu, X.; Hartwig, J. F. *Org. Lett.* **2003**, *5*, 1915.

Table 1. Pd-Catalyzed α-Arylation of (*S*,*S*)-**I** Using Ligand **L6**[a]



entry	X	Ar	Product	Yield (%)	de (%)[b]
1	I		**1**	86	97
2[b]	Br		**2**	96	99
3	Br		**3**	95	98
4	Br		**4**	96	94
5	Br		**5**	85	99
6[b,c]	Br		**6**	77	93
7	Br		**7**	98	98
8	Br		**8**	90	97
9	Br		**9**	93	97
10	Br		**10**	95	99
11	Br		**11**	98	99
12[b,c]	Br		**12**	92	74
13	Br		**13**	98	82

[a] Reaction conditions: 2.3 mmol of dioxolane **I**, 1 mmol of ArX, 2 mol % of $Pd(OAc)_2$, 8 mol % of P(*t*-Bu)$_3$·HBF_4, 2.5 mmol of LHMDS in toluene (1 mL/0.25 mmol ArX), rt. Isolated yield are averages of two runs. [b] Diastereomeric ratio determined by HPLC. (*R*,*R*)-**I** and (*S*,*S*)-**I** gave similar results. [c] Reaction carried at 50 °C for 12 h.

the aromatic ring. It is noteworthy that ester, nitrile, ketal, thioether, ether, trifluoromethyl, halide, silyl, and heterocyclic moieties remain intact as evidenced by the high yields obtained.

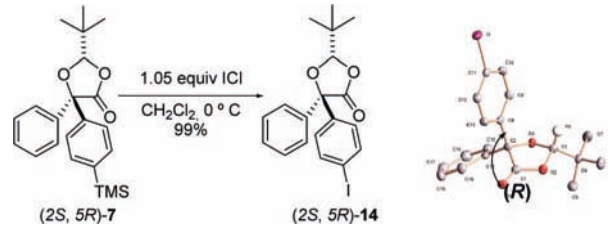
Hydrolysis of base-sensitive groups on the aryl bromide was not observed (Table 1, entries 4 and 9, 96% and 93% yield, respectively).

Coupling with bifunctional bromides such as 1-bromo-3-chlorobenzene and 2-bromo-5-chlorothiophene (Table 1, entries 8 and 13) occurred exclusively at the bromine. The conservation of the chloride group allows subsequent modification and is confirmed by the characteristic chlorine isotopic pattern in the mass spectra of these arylation products.

As shown in Table 1, the arylation shows high diastereoselectivity (93−99% de) using substituted halobenzenes (Table 1, entries 1−11). Yields remain high, but diastereoselectivities decrease for the heteroaryl bromides tested (entries 12 and 13). This fact could be explained by the role of secondary donor interactions in the Pd(II) intermediate due to the complexation ability of N and S atoms. Although these small interactions on the Pd catalytic species are deleterious in the sense of asymmetric induction, they are not strong enough to inactivate the catalyst. Despite the fact that metal-catalyzed asymmetric α-arylations are established and useful synthetic methods, the use of heteroaryl groups as coupling partners remains to date challenging.[18]

Diastereomeric excesses were determined by HPLC analysis. In all cases, only one isomer was observed by NMR spectroscopy (Table 1). Conversion of the trimethylsilyl moiety of (2*S*,5*R*)-**7** (Table 1, entry 7) to an iodine (2*S*,5*R*)-**14** provides a derivative whose configuration was crystallographically determined (Scheme 2). X-ray analysis found

Scheme 2. Synthesis of (2*S*,5*R*)-**14** and Its ORTEP Diagram

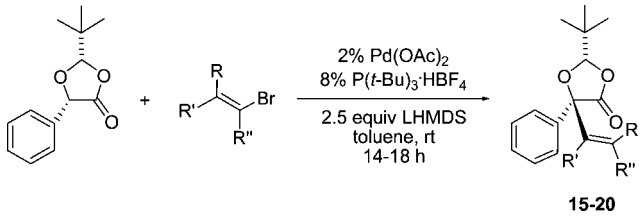


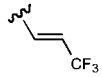
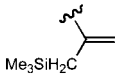
the relative and absolute configuration of compound **14** to be (2*S*,5*R*). This result is consistent with the approach of the aryl group moving toward the less hindered face of the chiral enolate and is in accordance with previously reported alkylations and allylations of dioxolane (*S*,*S*)-**I**.[9]

It is important to note that the conditions originally developed for arylation are also applicable to vinyl bromides of varying substitution pattern and geometry. In all cases, good yields and diastereoselectivities were achieved for the Pd-catalyzed vinylation of mandelic acid derivative **I**. The range of vinyl substrates includes α-branched, trisubstituted vinyl bromides and proceeds with retention of the double-bond configuration (as determined by coupling constants of the vinyl moiety by ^1H and ^{13}C NMR spectroscopy). In some cases, diastereomeric excesses were determined from the enantiomeric excesses of the corresponding diols (entries 4−6, Table 2).

The synthetic utility of these fully substituted mandelic acid derivatives is illustrated in Scheme 3. Reduction using $LiAlH_4$ proceeds in excellent yield at room temperature and leads to the synthesis of 1,2-diols with complete retention of configuration. Furthermore, the corresponding α-hydroxy acids could be obtained quantitatively via basic hydrolysis under mild conditions.

Table 2. Pd-Catalyzed α-Vinylation of (*S*,*S*)-**I** Using Ligand **L6**[a]



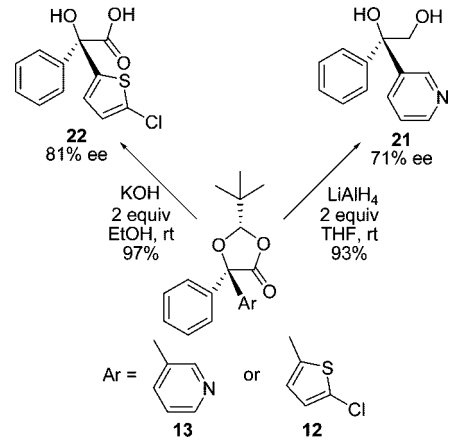
Entry	Vinyl	Product	Yield (%)	de (%)
1		**15**	94	94[b]
2[c]		**16**	99	96[e]
3[c]		**17**	78	93
4[c]		**18**	75	91[d]
5[c]		**19**	79	82[d]
6[c]		**20**	80	83[d]

[a] Reaction conditions: 2.3 mmol of dioxolane **I**, 1 mmol of vinyl halide, 2 mol % of $Pd(OAc)_2$, 8 mol % of $P(t\text{-}Bu)_3{\cdot}HBF_4$, 2.5 mmol of LHMDS in toluene (1 mL/0.25 mmol ArX), rt. Isolated yield in % and diastereomeric excess determined by HPLC are averages of two runs. [b] *Cis*/*trans* (90:10) mixture was used as starting material; product was also obtained as *cis*/*trans* (90:10) mixture. [c] **I**/vinyl bromide = 2:1. [d] ee determined by HPLC of the corresponding diol. [e] Reaction at 50 °C for 12 h. de determined by GC.

Diol **21** and hydroxy acid **22** coming from **12** and **13**, respectively, showed an ee in agreement with the de of the coupling products (see entries 12 and 13 in Table 1).

In summary, we have developed a new method for Pd-catalyzed α-arylation and -vinylation of a mandelic acid derivative under mild conditions. The high diastereoselectivities of these fully substituted, protected α-hydroxy acids result in high enantioselectivities when deprotected by hydrolysis or reduced to the corresponding acid or 1,2-diol. To conclude, we showed two examples of coupling using heteroaryl bromides in high yields and selectivities demonstrating that this new method could be extended to the coupling of these challenging moieties. Experiments for application in the synthesis of biologically active compounds are currently underway.

Scheme 3. Synthesis of Derivatives Starting from Coupling Products



Acknowledgment. S.J. sincerely thanks Prof. Steven Buchwald (MIT) for his support. This research was supported by NCI (L.J., T32CA09112) and DFG awards (S.W., WE 3549/2-1). We are grateful to Dr. Timothy Barder (MIT) for crystallographic analysis of (*2S*,*5R*)-**14**. The Bruker Advance 400 MHz spectrometer used in this work was purchased with funding from the National Institutes of Health (GM 1S10RR13886-01).

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

OL900131Q