# Amination, Aminocarbonylation, and Alkoxycarbonylation of Allenic/Propargylic Pd Intermediates Derived from Nonracemic Propargylic Mesylates: Synthesis of Nonracemic Propargyl Amines, Allenic Amides, and Butenolides

James A. Marshall* and Mark A. Wolf

*Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901*

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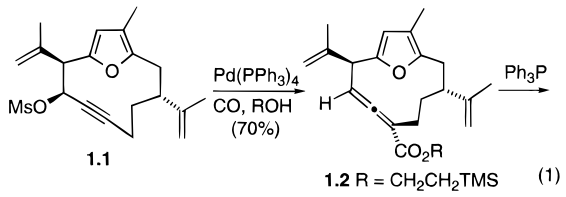
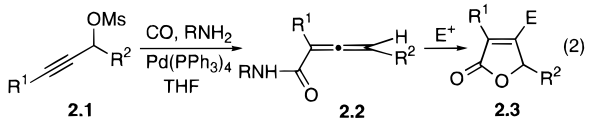
A key step in our recently reported total synthesis of kallolide A (**1.5**) was the efficient conversion of propargylic mesylate **1.1** to allenic ester **1.2** through Pd(0)-catalyzed alkoxycarbonylation with net inversion of configuration.[1] That this initial product was formed under kinetic control was demonstrated by its isomerization to the diastereomer **1.3** with $Ph_3P$. Butenolide formation was effected by cleavage of **1.3** with TBAF and treatment of the resulting acid **1.4** with catalytic $AgNO_3$.

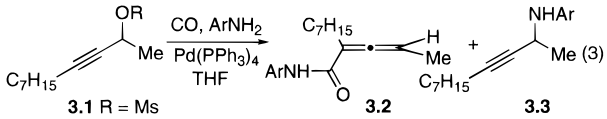



It was of interest to examine this chemistry in greater detail as a possible route to nonracemic allenic acid derivatives and butenolides. Initially, we looked into the feasibility of preparing allenic amides **2.2** as potential substrates for direct conversion to butenolides **2.3** in order to bypass the relatively sensitive allenic acid intermediates used in our previous sequence.[1,2]




Attempted amidocarbonylation of the racemic mesylate **3.1** with diethylamine, benzylamine, or *p*-fluorobenzylamine in the presence of CO (1 atm) and catalytic $Pd(PPh_3)_4$ (10 mol %) in THF at rt led to recovered mesylate and decomposition products.[3] No amide products could be detected. However, when the reaction was conducted with arylamines, the allenic amides **3.2** and the propargylic amines **3.3** were formed in high yield.

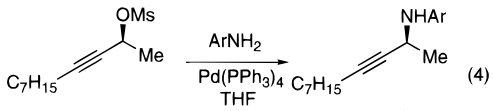
Increasing the pressure of CO led to an improvement in the ratio of amide to amine product. Higher ratios were also observed when the amine concentration was decreased from 0.1 to 0.05 M. Not surprisingly, the proportion of amine product **3.3** was found to be higher with the more nucleophilic anilines and vice versa.




| Ar | series | $P_{CO}$, psi | yield, % | **3.2**, % | **3.3**, % |
|---|---|---|---|---|---|
| Ph | **a** | atm | 78 | 26 | 74 |
| Ph | **a** | 120 | 72 | 62 | 38 |
| Ph | **a** | 120 | 70[a] | 73 | 27[a] |
| *p*-$MeC_6H_4$ | **b** | atm | 72 | 8 | 92 |
| *p*-$MeC_6H_4$ | **b** | 120 | 76 | 43 | 57 |
| *p*-$MeO_2CC_6H_4$ | **c** | atm | 80 | 94 | 6 |
| *p*-$MeO_2CC_6H_4$ | **c** | 120 | 80 | 100 | 0 |
| *p*-$ClC_6H_4$ | **d** | 120 | 70 | 99 | 1 |

[a] 0.05 M in amine; all others are 0.1 M

In the absence of CO, amines **4.2** were obtained from the nonracemic mesylate **4.1a** as the sole products of high ee, as determined by chiral HPLC.[4] The formation of propargylic substitution products such as **4.2** from propargyl/allenyl palladium complexes has rarely been observed.[5]




| Ar | **4.2** | t, h | yield, % | ee, % | $[\alpha]_D$ |
|---|---|---|---|---|---|
| Ph | **a** | 1 | 78 | 90 | -118.8 |
| *p*-$MeC_6H_4$ | **b** | 0.5 | 71 | 90 | -135.1 |
| *p*-$MeO_2CC_6H_4$ | **c** | 3 | 75 | 84 | -183.8 |
| *p*-$H_2NSO_2C_6H_4$ | **d** | 25 | 75 | - | -145.4 |
| *p*-$MeOC_6H_4$ | **e** | 0.75 | 75 | 90 | -123.3 |

Treatment of mesylate **4.1a**[6] with aniline in the absence of $Pd(PPh_3)_4$ afforded the propargylamine **5.1** of opposite rotation to that of amine **4.2a** secured in the Pd(0) reaction. It can therefore be surmised that the Pd(0)-catalyzed aminations proceed with retention of configuration.[7] In view of the ready availability of nonracemic propargylic alcohols,[6,8] the enantiodivergent preparation of propargylic amines of high ee from a single precursor holds significant synthetic potential.

Cyclization of the allenic carboxamide **3.2c** was effected with IBr.[9] However, subsequent hydrolysis of the result-

(1) Marshall, J. A.; Wallace, E. M. *J. Org. Chem.* **1995**, *60*, 796.

(2) We have found that saponification of allenic esters generally affords the acids in low yield. Carbonylation of propargylic mesylates in the presence of water and $Pd(PPh_3)_4$ gives the acids directly but proceeds in low to moderate yield.

(3) For aminations of $\pi$-allyl palladium species with aliphatic amines see, (a) Bäckvall, J-E.; Nordberg, R. E.; Zetterberg, K.; Akermark, B. *Organometallics* **1983**, *2*, 1625. (b)Baer, H. H.; Hanna, Z. S. *Can. J. Chem.* **1981**, *59*, 889. (c)Trost, B. M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3451.

(4) These amines were analyzed as their 3,5-dinitrobenzamide derivatives on a (*R,R*)-Whelk-O column.

(5) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589.

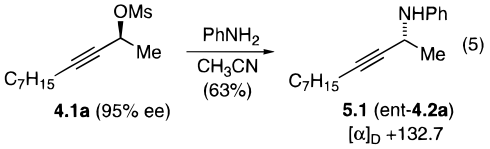
(6) Marshall, J. A.; Xie, S. J. Org. Chem. **1995**, *60*, 7230. Ku, Y. Y; Patel, R. R.; Elisseou, E. M.; Sawick, D. P. *Tetrahedron Lett.* **1995**, *36*, 2733.

(7) A possible pathway for this conversion would involve anti $S_N2'$-type oxidative addition of Pd(0) to the mesylate and subsequent anti $S_N2'$ attack by the amine on this allenyl Pd intermediate. *Cf.* Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103. Alternatively, the amine and CO may discriminate between equilibrating allenyl and propargyl Pd intermediates.

(8) *Cf.* Marshall, J. A.; Wang, X-j. *J. Org. Chem.* **1991**, *56*, 3211.

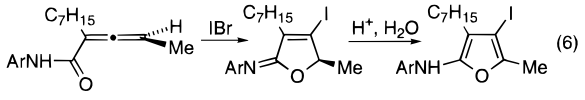
(9) *Cf.* Smith, A. B., III.; Duan, J. J.-W.; Hull, K. G.; Salvatore, B. A. *Tetrahedron Lett.* **1991**, *32*, 4855.

S0022-3263(96)00442-2 CCC: $12.00 




**4.1a** (95% ee) **5.1** (ent-**4.2a**) $[\alpha]_D$ +132.7

ing imino lactone **6.2** could not be effected. The sole isolable product was the interesting, but undesired, aminofuran **6.4**. The *p*-chloroanilide **3.2d** showed analogous behavior.

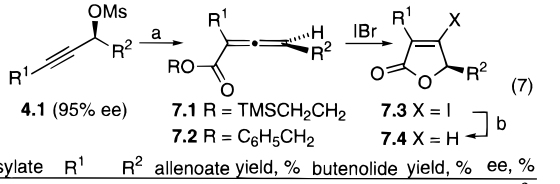



**3.2c**, Ar = *p*-$MeO_2CC_6H_4$ **6.2** (95%) **6.4**
**3.2d**, Ar = *p*-$ClC_6H_4$ **6.3** (96%) **6.5**

Accordingly, we turned our attention to the allenoate **7.1a**, obtained from mesylate **4.1a** by Pd(0)-catalyzed carbonylation in the presence of $\beta$-TMS ethyl alcohol, as a possible butenolide precursor.[10] Treatment with IBr led smoothly to the iodo lactone **7.3a**[11] which afforded butenolide **7.4a** in 70% yield (two steps) upon Pd(0)-catalyzed hydrogenolysis.[12] The alkoxycarbonylation of mesylate **4.1a** was effected with 5 mol % of the Pd catalyst. The use of 10 mol % led to partially racemized allenoate **7.1a** as evidenced by the optical rotation and chiral HPLC analysis.[13] The analogous carbonylations of propargylic mesylates **4.1b** and **4.1c** were effected with less than 1 mol % of catalyst.

Benzyl alcohol could also be employed in the alkoxycarbonylation sequence as illustrated by the formation of allenoates **7.2b** and **7.2c** from mesylates **4.1b** and **4.1c**.

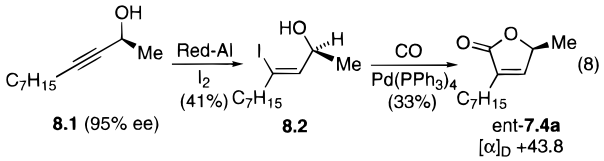
Hydrogenolysis of iodobutenolide **7.3a** to **7.4a** was effected with $Bu_3SnH$ and catalytic $Pd(PPh_3)_4$. An independent synthesis, as outlined in eq 8, afforded butenolide *ent*-**7.4a** of opposite rotation to that of **7.4a**.[14] Thus the Pd(0)-catalyzed carboxylation must proceed with inverson of configuration.[15] The stereochemistry of allenoates **7.1b** and **7.2b** is assigned by analogy.




**4.1** (95% ee) **7.1** R = $TMSCH_2CH_2$ **7.3** X = I
**7.2** R = $C_6H_5CH_2$ **7.4** X = H (b)

| mesylate | $R^1$ | $R^2$ | allenoate | yield, % | butenolide | yield, % | ee, % |
|---|---|---|---|---|---|---|---|
| **4.1a** | $C_7H_{15}$ | $CH_3$ | **7.1a** | 80 | **7.3a** | 85 | 80[c] |
| **4.1a** | $C_7H_{15}$ | $CH_3$ | **7.1a** | – | **7.4a**[d] | 70[e] | 82[f] |
| **4.1b** | H | $C_5H_{11}$ | **7.1b** | 80 | **7.3b** | 89 | 92[c] |
| **4.1b** | H | $C_5H_{11}$ | **7.2b** | 86 | **7.3b** | 93 | 95[c] |
| **4.1c** | $C_4H_9$ | H | **7.2c** | 76 | **7.3c** | 83 | – |

a. $Pd(PPh_3)_4$, CO, ROH; b. $Pd(PPh_3)_4$, $Bu_3SnH$; c. from HPLC analysis; d. $[\alpha]_D$ -38.0; e. based on **7.1a**; f. calculated from the rotation of ent-**7.4a**




**8.1** (95% ee) **8.2** ent-**7.4a** $[\alpha]_D$ +43.8

It is expected that these findings will be applicable to the syntheses of a wide range of nonracemic propargylic amines, allenic amides, and butenolides. Additional efforts in that direction will be reported in due course.

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**Supporting Information Available:** Representative experimental procedures and $^1H$ NMR spectra for all new compounds (37 pages).

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(10) The use of propargylic acetates or carbonates in these reactions gave low conversions to propargylic esters. *Cf.* Tsuji, J.; Sugiura, T.; Minami, I. *Tetrahedron Lett.* **1986**, *27*, 731. Interestingly, it has been reported that methoxycarbonylation of (*S*)-diethyl-1-ethynylpentyl phosphate affords methyl (*R*)-2,3-nonadienoate with retention of configuration.[5]

(11) $\beta$-TMS ethyl esters have rarely been employed in iodolactonizations. Considering the facile transformation of esters **7.1a** and **7.1b** to iodolactones **7.2a** and **7.2b**, it is likely that the methodology will be applicable to olefinic analogues, as well.

(12) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452.

(13) For a detailed study on the effect of Pd(0) concentration on racemization in $\pi$-allyl palladium intermediates, see Granberg, K. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 6858.

(14) For recent alternative routes to butenolides, *Cf.* Trost, B. M.; Muller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888. Hoye, T. R.; Humpal, P. E.; Jiménez, J. I.; Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.* **1994**, *35*, 7517. Buchwald, S. L.; Fang, Q.; King, S. M. *Tetrahedron Lett.* **1988**, *29*, 3445.

(15) An inversion pathway has been established for additions of organozinc compounds to propargyl/allenyl Pd(II) intermediates leading to allenes. Elsevier, C. J.; Kleijn, H.; Boersma, J.; Vermeer, P. *Organometallics* **1986**, *5*, 716.