ORGANIC LETTERS

2003
Vol. 5, No. 26
5015−5017

Further Utilization of Mucohalic Acids: Palladium-Free, Regioselective Etherification and Amination of α,β-Dihalo γ-Methoxycarbonyloxy and γ-Acetoxy Butenolides

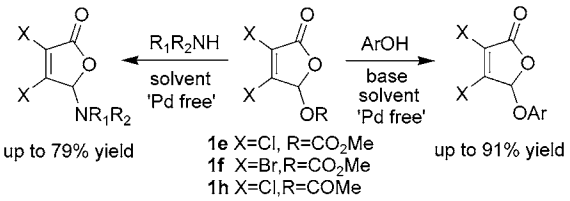
Peter G. Blazecka, Daniel Belmont, Tim Curran, Derek Pflum, and Ji Zhang*

Chemical Research and Development, Pfizer Global Research & Development, Ann Arbor Laboratories, Pfizer, Inc., 2800 Plymouth Road, Ann Arbor, Michigan 48105

ji.zhang@pfizer.com

Received October 13, 2003

ABSTRACT



Palladium-free etherification and amination of mucohalic acid methyl carbonates 1e (3,4-dichloro-5-methoxycarbonyloxy-5*H*-furan-2-one) and 1f (3,4-dibromo-5-methoxycarbonyloxy-5*H*-furan-2-one) and mucochloric acid acetate 1h (3,4-dichloro-5-acetoxy-5*H*-furan-2-one) was achieved to afford γ-functionalized α,β-unsaturated γ-butyrolactones in good to excellent yield.

Since Tsuji's first report of the palladium-mediated allylic alkylation many years ago,[1] this type of reaction has been extensively explored by Trost, Tsuji, and others[2] and has become an efficient and powerful method of forming carbon−carbon,[3] carbon−oxygen,[4] carbon−nitrogen,[5] and carbon−sulfur bonds.[6] Furthermore, this palladium-catalyzed Tsuji−Trost reaction has made catalytic asymmetric transformations possible. Recently, Trost finished an enantioselective total synthesis of (+)-aflatoxin B_1 and B_{2a} employing a chiral ligand in the etherification of butenolide **1b** to obtain key intermediate **2**.[7] A palladium-mediated enantioselective formation of an optically active sulfide by using a Helmchen−Pfaltz−Williams ligand was also reported.[8]

Perhaps the most important application of this methodology in medicinal chemistry is in carbon−nitrogen bond formation, i.e., allylic amination. Among the naturally occurring building blocks, nucleosides have played an increasingly important role in the expedition of novel and effective anti-HIV and antitumor agents. This is evident by the recent approval of Abacavir for the treatment of AIDS.

(1) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387.
(2) (a) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 593−649. (b) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (c) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. (d) Tsuji, J. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; pp 1669−1687.
(3) Tsuji, J.; Sato, K.; Okumoto, H. *Tetrahedron Lett.* **1982**, *23*, 5189. Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 3215.
(4) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276.
(5) Trost, B. M.; Patterson, D. E. *Chem. Eur. J.* **1999**, *5*, 3279. Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297. Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662.
(6) Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1992**, *33*, 8099. Trost, B. M.; Scanlan, T. S. *Tetrahedron Lett.* **1986**, *27*, 4141.
(7) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090.
(8) Frank, M.; Gais, H.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3353.

10.1021/ol035994n CCC: $25.00
Published on Web 12/03/2003

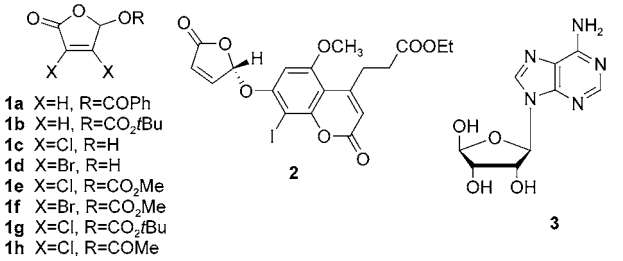
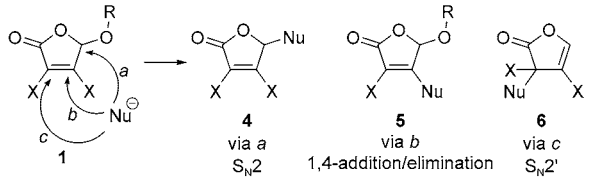


Figure 1. Masked γ-hydroxy butenolides and related biologically active compounds.

Synthetic and medicinal chemists have chosen natural antibiotic nucleosides such as Noraristeromycin (**3**) and their analogues as challenging targets.[9] Palladium-assisted routes to these compounds are well-documented and have recently been reviewed.[10] Considering the similarities between butenolide **1b** and mucohalic acid derivatives **1c** and **1d**, we imagined that a chemoselective reaction could be exploited for the preparation of novel nucleoside analogues. Therefore, we decided to study the application of **1c** and **1d** as building blocks.[11] Herein we report our initial results for the highly regioselective nucleophilic displacement of a masked mucohalic acid.

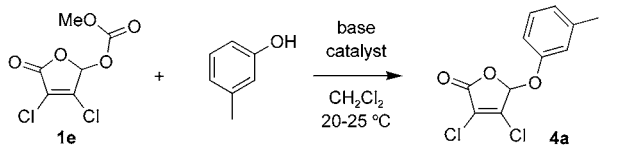
There are very few reported examples of selective manipulation of both allylic and vinylic functional groups within the same molecule. Many of these reports indicate that palladium catalysis is necessary for differentiation of allylic and vinylic units.[12] It is known that, due to the vinyl halides, masked mucohalic acids are very reactive toward different nucleophilic reagents and undergo a Michael-addition−elimination process (path *b* in Scheme 1).[13] Thus,

Scheme 1. Possible Nucleophilic Additions to **1**



any attempt at direct γ-substitution would seem without merit. A plausible way to overcome this hurdle would be to activate the γ-position via the formation of a π-allyl−Pd complex (from the corresponding carbonate or acetate). Therefore, Trost's etherification conditions (3% Pd_2dba_3 and 15% Cs_2CO_3)[7] were applied to mucochloric acid methyl carbonate (**1e**), which is easily prepared from **1c** in good yield.[14] Etherification of **1e** with *m*-cresol gives the desired product in excellent yield (Table 1, entry 1). A screening of

Table 1. Etherification under Different Reaction Conditions[a]



entry	catalyst	base	reaction time (h)	yield (%)[b]
1	3% Pd_2dba_3	15% Cs_2CO_3	4	83
2	3% Pd_2dba_3	none	65	nr[c]
3	3% Pd_2dba_3	20% CsF	7	87
4	3% Pd_2dba_3	20% KF	48	50
5	3% $Pd(PPh_3)_4$	15% Cs_2CO_3	2.5	69
6	none	15% Cs_2CO_3	0.5	75
7	none	15% Cs_2CO_3	7.5	87
8	none	50% Na_2CO_3	48	nr
9	none	20% CsF	7	89

[a] Reaction conditions: 1 equiv (2.0 mmol) of **1e**, 1.1 equiv of *m*-cresol, catalyst, base, 20 mL of CH_2Cl_2, room temperature. Reaction times were not optimized. [b] Isolated yields. [c] No reaction observed.

reaction conditions shows that a catalytic amount of base (15−20%) is essential for the reaction (Table 1, entry 2) and that Cs_2CO_3 or CsF gives the best results (Table 1, entries 1, 3, and 9). Upon noting the surprisingly short reaction times, the reaction was attempted in the absence of a palladium catalyst. Remarkably, these transformations proceeded equally as well (Table 1, entries 6, 7, and 9). To test the generality of this finding, the optimized etherification conditions were applied to **1e** employing a number of differently substituted phenols, with good to excellent results (Table 2).

In addition to **1e**, etherifications involving **1f**−**h** are equally successful. Interestingly, when mucochloric acid acetate (**1h**) is employed as the starting material (Table 2, entry 9), a catalytic amount of base (15−20%) is not completely effective, but rather 1 equiv is required to drive the reaction to completion.[15] This is a significant deviation from the methyl carbonate system. The reason for this deviation may be that in the carbonate system, the majority of the phenol is deprotonated by an alkoxy anion, generated in situ by decarboxylation of the displaced carbonate anion, while the acetate generated in situ from **1h** is not strong enough to deprotonate the phenol.

(9) Hegedus, L. S.; Hervert, K. L.; Matsui, S. *J. Org. Chem.* **2002**, *67*, 4076. Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1996**, *118*, 3037.

(10) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875 and references therein.

(11) Zhang, J.; Blazecka, P. G.; Berven, H.; Belmont, D. *Tetrahedron Lett.* **2003**, *44*, 5579. Zhang, J.; Blazecka, P. G.; Davidson, J. G. *Org. Lett.* **2003**, *5*, 553. Zhang, J.; Blazecka, P. G.; Belmont, D.; Davidson, J. G. *Org. Lett.* **2002**, *4*, 4559.

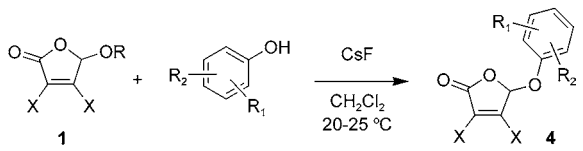
(12) (a) Organ, M. G.; Arvanitis, E. A.; Villani, A.; Majkut, Y.; Hynes, S. *Tetrahedron Lett.* **2003**, *44*, 4403. (b) Organ, M. G.; Arvanitis, E. A.; Dixon, C. E.; Cooper, J. T. *J. Am. Chem. Soc.* **2002**, *124*, 1288. (c) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057. (d) Nwokogu, G. C. *J. Org. Chem.* **1985**, *50*, 3900.

(13) Sulikowski, G. A.; Agnelli, F.; Corbett, R. M. *J. Org. Chem.* **2000**, *65*, 337. Moore, H. W.; Hernandez, L., Jr.; Kunert, D. M.; Mercer, F.; Sing, A. *J. Am. Chem. Soc.* **1981**, *103*, 1769.

(14) For preparation of **1e**−**h**, see Supporting Information.

(15) For a recent example of transition-metal-free Tsuji−Trost-type reactions of an allylic acetate in polar protic media, see: Chevrin, C.; Le Bras, J.; Hénin, F.; Muzart, J. *Tetrahedron Lett.* **2003**, *44*, 8099.

Table 2. Etherification under Optimized Reaction Conditions[a]



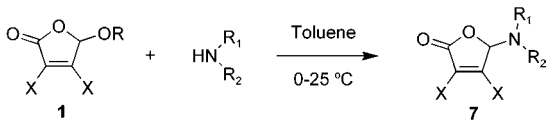
entry	X	R	R_1; R_2	reaction time (h)	4	yield (%)[b]
1	Cl	CO_2Me	*p*-OMe; H	7	**b**	91
2	Cl	CO_2Me	3-OCH_2O-4	7	**c**	86
3	Cl	CO_2Me	H; H	7	**d**	88
4	Cl	CO_2Me	*m*-F; H	23	**e**	72
5	Cl	CO_2Me	3-Cl, 5-Cl	23	**f**	70
6	Cl	CO_2Me	*m*-Br; H	24	**g**	62
7	Br	CO_2Me	*m*-Me; H	6	**h**	91
8	Cl	CO_2tBu	*m*-Me; H	6	**a**	81
9	Cl	COMe	*m*-Me; H	22	**a**	75[c]

[a] Reaction conditions: 1 equiv (2.0 mmol) of **1**, 1.1 equiv of substituted phenol, 0.20 equiv CsF, 20 mL of CH_2Cl_2, room temperature. Reaction times were not optimized. [b] Isolated yields. [c] Used 1.1 equiv CsF.

This reaction can be viewed as a simple nucleophilic substitution.[16] Thus, in contrast to a great number of reports regarding etherification of allylic carbonates, palladium is not required for the mucohalic acid system. A palladium-free process would be of significant benefit in the later stages of drug development.[17] While some asymmetric π-allyl palladium reactions compete with uncatalyzed background reaction, more often the concentration of the π-allyl palladium species is decreased in order to increase the enantioselectivity.[18] This indicates that in general, the uncatalyzed reaction is quite slow; however, in this system, the palladium-free reaction is as fast as the catalyzed reaction.

Unlike many palladium-free processes, where other transition metals such as copper salts and iridium complexes are used,[19,20] under our palladium-free conditions, nucleophilic displacement of **1e** with benzylamine successfully gives the γ-substitution product **7a** in good yield without using other transition metals (Table 3, entry 1). Furthermore, reactions of **1e**, **1f**, and **1h** with select amines under similar conditions give moderate to good yields of the amination products. Although reaction of **1e** with aniline fails to give the γ-substitution product,[21, 22] a simple change to a more polar solvent (NMP) results in an excellent yield of **8** (Scheme 2). Thus, by careful choice of reagents and reaction conditions, masked mucohalic acids can be converted to desired products by nucleophilic substitution in a highly regioselective manner. With this ability to control regiochemistry and reactivity, one might view this masked mucohalic acid as a useful tool for custom designed synthesis. Since the Br and Cl atoms at the α- and β-positions are unaffected under these reaction conditions, they remain available for further transformations.

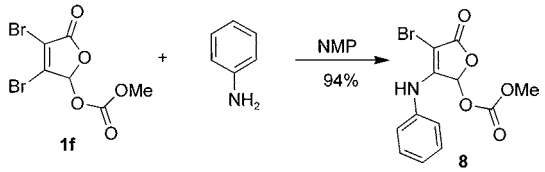
Table 3. Amination under Different Reaction Conditions[a]



entry	X	R	R_1; R_2	reaction time (h)	7	yield (%)[b]
1	Cl	CO_2Me	Bn; H	5	**a**	79
2	Cl	CO_2Me	allyl; H	2	**b**	74
3	Cl	CO_2Me	*n*Pr; *n*Pr	17	**c**	61
4	Cl	COMe	*n*Pr; *n*Pr	25	**c**	54
5	Br	CO_2Me	Bn; H	5	**d**	65
6	Cl	COMe	Bn; H	8	**a**	46

[a] Reaction conditions: 1 equiv (2.0 mmol) of **1**, 1.0−2.0 equiv of amine, 20 mL of toluene, 2−17 h, 0 °C to room temperature. Reaction conditions were not optimized. [b] Isolated yields.

Scheme 2. Example of 1,4-Addition/Elimination Reaction



In summary, we have found conditions to selectively control reaction of compounds of the type **1e**−**h** at the β- and γ-positions. This is a palladium-free process and is catalyzed by weak base under mild reaction conditions. Further investigation, including mechanistic study and extension of the use of these building blocks, will be reported in due course.

Acknowledgment. We thank Dr. James G. Davidson for his encouragement and continued support of this work.

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

OL035994N

(16) For a review of nucleophilic and organometallic displacement reactions of allylic compounds, see: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.

(17) Expensive nature of palladium reagents and any associated difficulties in attaining FDA-acceptable residual levels of palladium could significantly add to the cost of products made by using these reagents.

(18) For example, see: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. (c) Ref 7.

(19) Ma, D.; Xia, C.; Jiang, J.; Zhang, J.; Tang, W. *J. Org. Chem.* **2003**, *68*, 442. Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 4727. Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.

(20) López, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426.

(21) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164.

(22) Tanimori, S.; Inaba, U.; Kato, Y.; Kirihata, M. *Tetrahedron* **2003**, *59*, 3745.