ORGANIC LETTERS

2002
Vol. 4, No. 5
863−865

Amidoglycosylation via Metal-Catalyzed Internal Nitrogen Atom Delivery

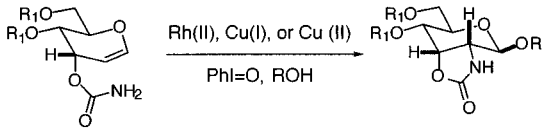
Elana Levites-Agababa, Elnaz Menhaji, Lisa N. Perlson, and Christian M. Rojas*

Department of Chemistry, Barnard College, 3009 Broadway, New York, New York 10027

crojas@barnard.edu

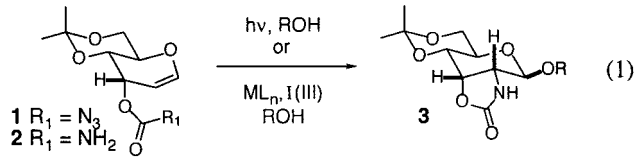
Received January 28, 2002

ABSTRACT



Rhodium and copper acyl nitrenoids are likely intermediates in amidoglycosylation reactions of allal 3-carbamates. Iodine(III)-mediated nitrenoid formation, interaction of this species with the glycal enol ether π-system, and highly β-stereoselective glycosylation occur in a one-pot process that requires no additional Lewis acid activation.

Directed nitrogen insertion reactions offer exciting opportunities for substrate control of chemo-, regio-, and stereoselectivity in carbon−nitrogen bond formation. In applying this strategy to the synthesis of 2-amino sugars from glycal precursors,[1] we initially investigated photochemical reactions of azidoformate **1** (eq 1).[2] Although conversion to



(1)

products **3** was achieved, the highly reactive nature of the intermediate acyl nitrene hampered the process, prompting us to consider a metallanitrene as the reactive nitrogen fragment. While transition metal carbenoids generated from α-diazocarbonyl compounds have been intensively investigated in reactions such as C−H insertion and C=C addition,[3] the corresponding acyl nitrenoids have received much less attention.[4] Their formation is complicated by the possibility of Curtius-type rearrangement and by the resistance of acyl azides to metal-promoted decomposition. As a result, sulfonyl nitrenoids have predominated for nitrogen atom transfer.[5] The use of acyl nitrenoids offers a valuable synthetic complement by facilitating intramolecular reactions, and in many cases the *N*-acylated products will be more readily manipulated than the corresponding sulfonamides.

We now communicate realization of intramolecular nitrogen atom delivery, apparently via rhodium and copper acyl nitrenoids, in amidoglycosylation reactions of allal carbamates **2** and **5**. Iodine(III)-mediated nitrenoid formation, interaction of this species with the enol ether π-system, and highly stereoselective glycosylation occur in a one-pot process (eq 1) that requires no additional Lewis acid activation.

(1) For various routes toward 2-amino sugars from glycals, see: (a) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244. (b) Leblanc, Y.; Fitzsimmons, B. J.; Springer, J. P.; Rokach, J. *J. Am. Chem. Soc.* **1989**, *111*, 2995. (c) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811. (d) Lafont, D.; Boullanger, P.; Carvalho, F.; Vottero, P. *Carbohydr. Res.* **1997**, *297*, 117. (e) Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179. (f) Di Bussolo, V.; Liu, J.; Huffman, L. G., Jr.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 204. (g) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2525.

(2) Kan, C.; Long, C. M.; Paul, M.; Ring, C. M.; Tully, S. E.; Rojas, C. M. *Org. Lett.* **2001**, *3*, 381.

(3) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998.

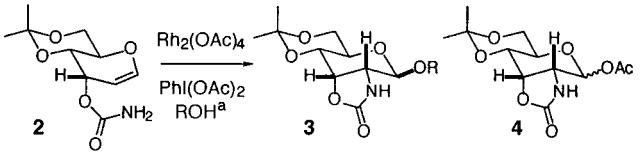
(4) For example: (a) Groves, J. T.; Takahashi, T. *J. Am. Chem. Soc.* **1983**, *105*, 2073. (b) Du Bois, J.; Hong, J.; Carreira, E. M.; Day, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 915. (c) Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179. (d) Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *Acc. Chem. Res.* **1997**, *30*, 364. (e) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598.

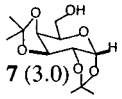
(5) Müller, P. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 2, pp 113−151.

10.1021/ol025634k CCC: $22.00
Published on Web 02/08/2002

A recent report described the use of iodobenzene diacetate, $PhI(OAc)_2$, and catalytic dirhodium(II) carboxylates in acyl nitrenoid generation from primary carbamates, leading to intramolecular C−H insertion.[4e] Application of these conditions to carbamate **2**[6] provided an anomeric mixture[7] of 2-amido glycosyl acetates **4** (Table 1, entries 1 and 2). In the absence of Rh(II) catalyst, the starting carbamate was recovered unchanged. Mindful of separate reports detailing (1) the use of $PhI(OAc)_2$ in acid-promoted reactions with glycals[8] and (2) the Lewis acidic properties of Rh(II) carboxylates,[9] we also verified that a model glycal, tri-*O*-acetyl-D-glucal, failed to react with $PhI(OAc)_2$ in the presence of $Rh_2(OAc)_4$. These results were consistent with reaction of **2** via a rhodium-complexed nitrene rather than through initial activation of the glycal C=C unit by the iodine(III) reagent.

Table 1. Rhodium-Catalyzed Amidoglycosylation with $PhI(OAc)_2$



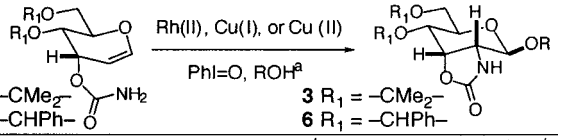
Entry	ROH (equiv)	Equiv $Rh_2(OAc)_4$	Product **3**[b] (% Yield[c])	%Yield **4**[c] (β:α)[d]
1	None	0.1	—	64 (3.0:1)
2	None	0.05	—	64 (2.3:1)
3	 **7** (3.0)	0.3	**3a** (19)	47 (15:1)
4	*i*-PrOH (5.0)	0.1	**3b** (34)	40 (9:1)
5	*i*-PrOH (25)	0.2	**3b** (67)	—
6[e]	EtOH (25)	0.2	**3c** (75)	—
7[e]	MeOH (25)	0.2	**3d** (75[f])	—

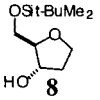
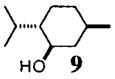
[a] Typical reaction conditions: $PhI(OAc)_2$ (1.5 equiv), MgO (5 equiv), CH_2Cl_2, 40 °C, 18−24 h. [b] Only the β-products were observed. [c] Isolated yield after silica gel chromatography. [d] Anomeric ratio determined by ^1H NMR analysis of the glycosyl acetates mixture. [e] Additional $PhI(OAc)_2$ (0.7−1.0 equiv) was added. [f] Combined yield for a 3.2:1 mixture of **3d** and its *N*-hydroxymethyl derivative.

A large excess of alcohol suppressed formation of the glycosyl acetates **4**, leading to isolation of β-2-amido allopyranosides **3b**−**d** in good yields (Table 1, entries 5−7). Remarkably, the glycosyl acceptor did not interfere with events leading to C2−N bond formation.[10]

To curtail the amount of alcohol required, we turned to iodosobenzene (PhI=O)[11] to form the presumed imino-iodinane intermediate (vide infra). Indeed, rhodium(II) catalysis provided amidoglycosylation, using iodosobenzene in place of $PhI(OAc)_2$ (Table 2, entries 1−5). Under these conditions, much smaller amounts of glycosyl acceptor were required to realize synthetically useful yields for the tandem amidation-glycosylation process. While 5 equiv of acceptor were typically employed to boost yields, most of the surplus could be recovered upon chromatography. For example, all but 1.5 equiv of ribose-derived secondary alcohol **8** was recovered after reaction with carbamate **2**. In various instances we isolated trace amounts of the α-products, confirming the extremely high level of β-selectivity in the glycosylation.

Table 2. Use of PhI=O in Rh- and Cu-catalyzed Amidoglycosylations



Entry	Allal	ROH	Catalyst[b] (equiv)	Product (% Yield[c])	β:α[d]
1	**2**	*i*-PrOH	A (0.1)	**3b** (75)	β only
2	**2**	**7**	A (0.1)	**3a** (58)	>20:1
3	**2**	 **8**	A (0.1)	**3e** (47[e])	>10:1
4	**2**	 **9**	A (0.1)	**3f** (65[f], 71[g])	>35:1
5	**5**	**9**	A (0.1)	**6a** (63[h])	>50:1
6[i]	**2**	*i*-PrOH	B (0.2)	**3b** (47)	β only
7[i]	**5**	*i*-PrOH	B (0.2)	**6b** (38)	β only
8	**2**	**9**	C (0.2)	**3f** (49[j])	>20:1

[a] Typical reaction conditions: ROH (5 equiv), PhI=O (1.8−2.0 equiv), 4 Å molecular sieves, CH_2Cl_2, 23 °C, 18−25 h. [b] Catalysts: A, $Rh_2(OAc)_4$; B, $Cu(MeCN)_4PF_6$; C, $Cu(acac)_2$. [c] Isolated yield after silica gel chromatography. Where the C1−C2 oxidative cleavage byproduct (see **14**, Scheme 1) was inseparable, the reported yield has been corrected on the basis of ^1H NMR integration. [d] Ratio based on isolated yields of the separated anomers. [e] C1−C2 cleavage byproduct (13%) was isolated separately. [f] 12:1 mixture with C1−C2 cleavage byproduct. [g] Obtained with freshly prepared PhI=O. 17:1 mixture with C1−C2 cleavage byproduct. [h] 20:1 mixture with C1−C2 cleavage byproduct. [i] Acetonitrile solvent, 1−3 h. [j] 28:1 mixture with C1−C2 cleavage byproduct.

Alcohols could be included in the reaction mixture, leading directly to glycosides **3**, but acetates **4** also formed, even when up to 5 equiv of the alcohol was present (Table 1, entries 3 and 4). Notably, only the β-C1 stereochemistry[7] was observed in products **3**, while the acetates **4** were substantially enriched in the β-anomer. The glycosyl acetates were not intermediates in the formation of glycosides **3**; submission of isolated **4** to the reaction conditions with 2-propanol neither yielded glycosylated product **3b** nor altered the anomeric composition of the recovered acetates.

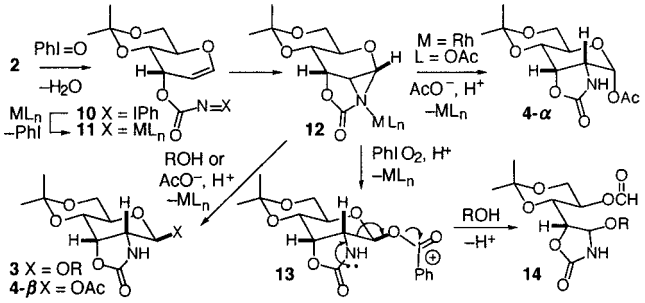
(6) For preparation of **2** and **5** see Supporting Information.
(7) See Supporting Information for details of anomeric stereoassignments.
(8) Shi, L.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 6939.
(9) Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc.* **2001**, *123*, 5366.
(10) With ethanol or methanol, some of the $PhI(OAc)_2$ was consumed in oxidation of the alcohol. In the latter case, formaldehyde was trapped, forming the *N*-hydroxymethyl derivative of **3d**, which was inseparable from **3d** but could be removed as its *tert*-butyl carbonate. See Supporting Information for details.
(11) While this reagent lacked efficacy in the Du Bois C−H insertion chemistry,[4e] its use in inter- and intramolecular aziridination reactions of sulfonamides with Cu(I) or Cu(II) has been described: Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707.

Metal nitrenoid-mediated amidoglycosylation was also feasible starting from either Cu(I) or Cu(II) sources (Table 2, entries 6−8). Although yields in this particular application were lower with copper catalysis, the possibility of using copper ions with asymmetric ligands[12] offers clear opportunities for enantioselective reactions of acyl nitrenoids.

In the absence of catalyst, treatment of carbamate **2** with iodosobenzene and 2-propanol provided a small quantity (16% yield) of β-isopropyl-2-amido allopyranoside **3b**, along with recovery of unreacted carbamate (38%). This much less efficient process is attributable to reaction of the glycal double bond with either the iminoiodinane or the derived nitrene.[13]

A plausible mechanistic scenario for the metal-catalyzed amidoglycosylation process is outlined in Scheme 1. Formation of iminoiodinane **10** in the presence of molecular sieves is consistent with the work of Dauban and Dodd on copper nitrenoids originating from in situ iodine(III) oxidation of sulfonamides.[11] Catalyst-promoted loss of iodobenzene from **10** would lead to metallanitrene **11**,[14] and reaction with the glycal double bond provides metal−aziridine complex **12**.[15] Internal acetate transfer in **12** would yield **4**-α. The presence of alcohols may dissociate the metal from complex **12**, lowering the proportion of α-acetoxy product in the $PhI(OAc)_2$-mediated reactions (compare, for example, entries 1 and 3, Table 1). External nucleophilic opening of the aziridine, in either its metal-complexed (**12**) or metal-free form, would account for the highly stereoselective glycosylation to **3** or **4**-β.

Scheme 1



We detected small quantities of formate ester byproducts **14** (Scheme 1), corresponding to oxidative cleavage of the C1−C2 bond (Table 2, entries 3−5, 8). Use of fresh iodosobenzene[16] decreased the amount of oxidative cleavage. Iodosobenzene disproportionates to iodobenzene and $PhIO_2$,[17] and this iodine(V) species may provide the side reaction, possibly as indicated in Scheme 1 for the conversion of **12** to **14**.[18]

In summary, rhodium- and copper-catalyzed amidoglycosylation of alcohols occurs readily from allal 3-carbamates in the presence of iodosobenzene. Sequential C2−N bond formation and β-selective glycosylation may take place via a metal-complexed glycosyl aziridine. Further mechanistic investigations and application of acyl nitrenoid methodology to other glycal scaffolds[19] and to natural products synthesis are underway.

Acknowledgment. We are grateful for generous financial support from the National Institutes of Health, Research Corporation, and the Petroleum Research Fund. The Barnard NMR facility is supported by the National Science Foundation.

Supporting Information Available: Experimental procedures, details of anomeric stereoassignments, and characterization data for **2**, **5**, and all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025634K

(12) (a) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.

(13) For examples of iodine(III)-induced Hofmann rearrangements of primary amides, see: (a) Moriarty, R. M.; Chany, C. J., II; Vaid, R. K.; Prakash, O.; Tuladhar, S. M. *J. Org. Chem.* **1993**, *58*, 2478. (b) Yu, C.; Jiang, Y.; Liu, B.; Hu, L. *Tetrahedron Lett.* **2001**, 42, 1449.

(14) Reaction via a metal complex that retains a N−I connection is another mechanistic possibility. For discussions, see: (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889.

(15) A metal−aziridine complex has been identified computationally as a possible resting state in Cu-catalyzed alkene aziridination: Brandt, P.; Södergren, M. J.; Andersson, P. G.; Norrby, P.-O. *J. Am. Chem. Soc.* **2000**, *122*, 8013. Alternatively, a metallaazetidine might form, providing **4**-α upon reductive elimination and **3**/**4**-β via nucleophilic opening of the metallacycle at C1.

(16) Saltzman, H.; Sharefkin, J. G. In *Organic Syntheses*; Baumgarten, H. E., Ed.; John Wiley & Sons: New York, 1973; Vol. 5, pp 658−659.

(17) Banks, D. F. *Chem. Rev.* **1966**, *66*, 243.

(18) For examples of C−C cleavage and rearrangements promoted by I(V) and I(III), see: (a) De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272. (b) Engstrom, K. M.; Mendoza, M. R.; Navarro-Villalobos, M.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1128.

(19) Intramolecular cyclopropanation of glucals has been reported recently: Yu, M.; Lynch, V.; Pagenkopf, B. L. *Org. Lett.* **2001**, *3*, 2563. For intramolecular amidation of glucals and galactals using *N*-centered radicals, see ref 1g.