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Copper-Catalyzed Iminoiodane-Mediated Aminolactonization of Olefins: Application to the Synthesis of 5,5-Disubstituted Butyrolactones

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ABSTRACT

A copper(I)-catalyzed reaction of a variety of 4-aryl-pent-4-enoates with nosyliminoiodane generated *in situ* provides the corresponding 5-aryl-5-nosylamidomethylbutyrolactones. The reaction presumably proceeds *via* an aziridine intermediate, which could be isolated in one case.

The metal-catalyzed generation of nitrenes from the hypervalent iodine arylsulfonyliminoiodane reagents Ar-SO_2N=IPh allows direct, mild, and generally high-yielding formation of aziridines from olefins.[1] Originally described by Mansuy using metalloporphyrins as the catalysts,[2] a thorough investigation of this reaction was conducted by Evans and co-workers who established that copper salts were the most effective in generating the reactive metallanitrene species from the iminoiodanes.[3] Enantioselective aziridinations, at least of the styrene-type olefins, could furthermore be accomplished by including chiral ligands, such as BOX ligands[4] or diimines,[5] in the reaction mixture.

The advent of one-pot procedures,[6] in which the iminoiodane is generated directly in solution, considerably improved the operational ease of this aziridination technique since the tedious and sometimes delicate prior preparation of the relatively unstable iminoiodanes was no longer necessary (Scheme 1). The synthetic importance of

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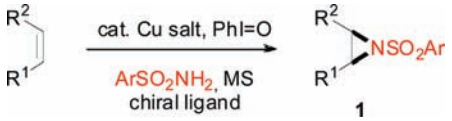
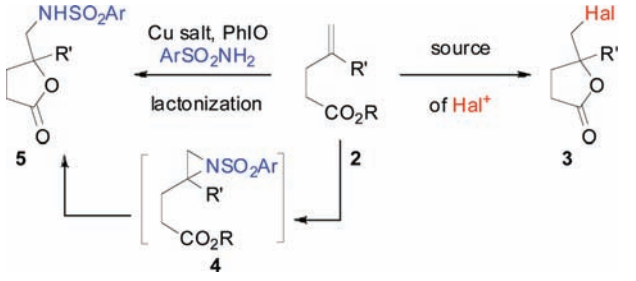
this aziridination procedure is reflected by its application to an ever-growing list of natural product total syntheses.[7]

Scheme 1. Asymmetric Copper-Catalyzed Iminoiodane-Mediated Aziridination



Halolactonization of olefinic carboxylic acids or esters is a well-known method for obtaining 5-halomethyl-γ-lactones and particularly *gem*-disubstituted γ-lactones.[8] Thus, treatment of a compound such as **2** (R′ = Me) with a source of I^+ gives the 5-iodomethyl-5-methyl-γ-lactone **3** (Hal = I, Scheme 2). This type of reaction has been utilized in a wide variety of synthetic strategies toward natural or biologically active compounds.[9] While substrate-controlled stereoselective halolactonizations have been well-described, recent research in this area has focused on the development of reagent-controlled stereoselectivity. It occurred to us that, by analogy with this halolactonization reaction, aziridination of the same type of substrate, that is, an olefinic ester or carboxylic acid **2,** should follow a similar route to give, after initial formation of the aziridine **4**, amidomethyl-γ-lactones of type **5** (Scheme 2). No reports of such an aminolactonization reaction have, to the best of our knowledge, been described.

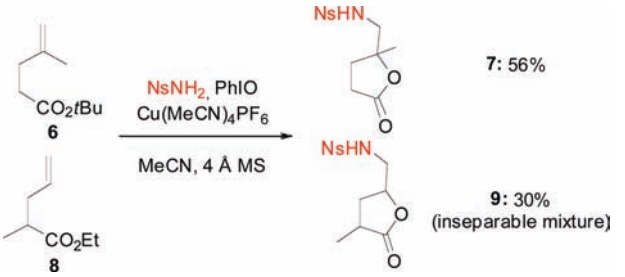
Scheme 2. Halolactonization vs Aminolactonization



In order to test our hypothesis, *tert*-butyl 4-methyl-4-pentenoate **6** was subjected to the one-pot aziridination procedure. Thus, to our delight, reaction of **6** with 1.2 equiv each of nosylamide and iodosylbenzene in acetonitrile in the presence of 25 mol % of tetrakisacetonitrile hexafluorophosphate copper salt successfully provided 5-methyl-5-nosylamidomethylbutyrolactone **7** in 56% yield with no trace of the intermediate aziridine (Scheme 3).

This aminolactonization reaction was then successfully extended to the β-methyl analogue **8** in the form of its ethyl

Scheme 3. Aminolactonization of Unsaturated Esters



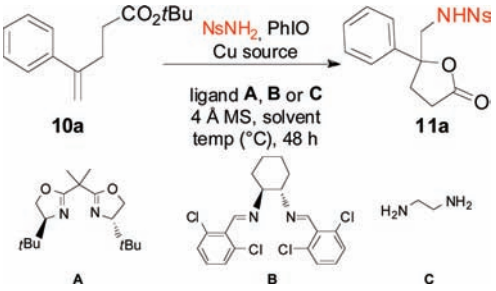
ester. The corresponding lactone **9** was, however, obtained with a lower yield of 30% as an inseparable 1:1 mixture of diastereoisomers. While the above reactions provided proof-of-concept regarding the viability of this novel aminolactonization reaction, the relatively low yields of product can be attributed to the well-documented difficulty of this aziridination reaction when applied to terminal olefins.[1]

With the objective of obtaining 5,5-disubstituted γ-lactones, the above considerations encouraged us to attempt the aminolactonization reaction starting from styrene precursors known to be more reactive toward this aziridination procedure. Thus, *tert*-butyl styrene-1-propanoate **10a** was prepared in 94% yield by Suzuki–Miyaura coupling of *tert*-butyl 4-bromo-4-pentenoate with phenylboronic acid (see Supporting Information). Surprisingly, when compound **10a** was subjected to the same one-pot aziridination procedure used for the formation of lactone **7**, only starting material was recovered with no evidence of formation of either the **10a**-derived aziridine or aminolactone **11a** (Table 1, entry 1). However, when the reaction was conducted in the presence of 12 mol % of chiral BOX ligand **A**, a very satisfactory yield of 90% of the 5-phenyl-5-nosylamidomethyl-butyrolactone **11a** was obtained though with an ee of only 48% (entry 2).[10] That an amino ligand was necessary to allow the reaction to proceed was demonstrated by replacement of the chiral BOX ligand by achiral ethylenediamine (ligand **C**) which also provided aminolactone **11a**, though in somewhat lower yield (72%, entry 3). Attempts were then made to optimize the yields of this reaction. Changing the solvent to dichloromethane or benzene led in both cases to substantial decreases in yield (51% and 25%, respectively) and ee's (4% and 20%) (entries 4 and 5) as did running the reaction at 0 or −25 °C (entries 6 and 7). The same observation was made when the $Cu(MeCN)_4PF_6$ catalyst was replaced by $Cu(PhCN)_4ClO_4$ or $(CF_3SO_3)_2Cu$ (entries 8 and 9). Finally, use of diimine **B** as a chiral ligand provided a high yield of **11a** (83%) but an almost negligible ee (5%, entry 10). BOX ligand **A** was thus used in all the subsequent reactions since yields were higher than with ligand **B** or **C**.

(9) (a) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, 171–197. (b) Rousseau, G.; Robin, S. *Tetrahedron* **1998**, *54*, 13681–13736. (c) Hauske, J. R.; Julin, S. M. *Tetrahedron Lett.* **1993**, *34*, 4909–4912. (d) Jung, M.; Ham, J.; Song, J. *Org. Lett.* **2002**, *4*, 2763–2765. (e) Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett.* **2002**, *4*, 1343–1345.

(10) Because the BOX ligands of type **A** as well as the salens of type **B** are more adapted to stereoselective aziridination of 2- rather than 1-substituted styrenes, no further attempts were made to improve the ee's of the reactions described herein.

Table 1. Optimization of Aminolactonization Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	ligand	yield (ee) [%]
1	$Cu(MeCN)_4PF_6$	MeCN	rt	–	–
2	$Cu(MeCN)_4PF_6$	MeCN	rt	**A**	90 (48)
3	$Cu(MeCN)_4PF_6$	MeCN	rt	**C**	72 (00)
4	$Cu(MeCN)_4PF_6$	CH_2Cl_2	rt	**A**	51 (04)
5	$Cu(MeCN)_4PF_6$	C_6H_6	rt	**A**	25 (20)
6	$Cu(MeCN)_4PF_6$	MeCN	0	**A**	68 (35)
7	$Cu(MeCN)_4PF_6$	MeCN	−25	**A**	63 (33)
8	$Cu(PhCN)_4ClO_4$	MeCN	rt	**A**	69 (24)
9	$(CF_3SO_3)_2Cu$	MeCN	rt	**A**	35 (10)
10	$Cu(MeCN)_4PF_6$	MeCN	rt	**B**	83 (05)

[a] All reactions were carried out with 1.2 equiv of $NsNH_2$, 1.2 equiv of PhIO, 10 mol % [Cu], and 12 mol % ligand with 4 Å molecular sieves.

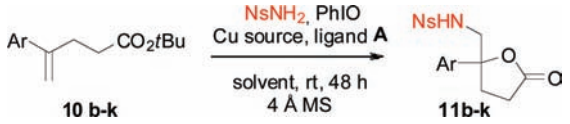
To test the generality of this novel aminolactonization reaction, the optimized conditions of Table 1 were applied to a series of phenyl-substituted analogues **10** all prepared in good to excellent yields by Suzuki−Miyaura coupling (see Supporting Information). Compounds **10b**−**k** were then subjected to our standard aziridination/lactonization conditions. As shown in Table 2, the *o*-, *m*-, and *p*-methoxy derivatives **10b**−**d** all gave excellent yields (83%, 91%, 86%) of the corresponding 5,5-disubstituted butyrolactones **11b**−**d**, respectively (entries 1−3). Similarly, the presence of three methoxy groups or an *o*-fluorine atom on the aryl ring (**10e**, **10g**) provided excellent yields of the corresponding lactones **11e** (93%) and **11g** (79%), respectively (entries 4 and 6).

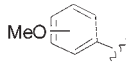
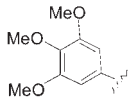
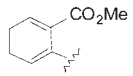
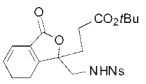
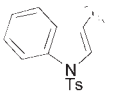
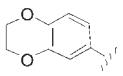
In the case of derivative **10f**, only compound **11f** was isolated in 72% yield as a result of competitive opening of the intermediate aziridine by the adjacent *o*-methyl ester (entry 5). The furan, thiophene, and indole derivatives **10h**−**j** gave a slightly lower but acceptable yield of the corresponding 5-heterocycle-substituted lactones **11h**−**j** (69%, 64%, and 62% yields, respectively, entries 7−9). Finally, the ethylenedioxy derivative **10k** afforded lactone **11k** in 77% yield (entry 10).

The optimized aziridination/lactonization reaction conditions were also successfully extended to a variety of olefinic substrates **12a**−**f**, all prepared by Suzuki−Miyaura coupling of the appropriate starting materials (see Supporting Information).

Thus, extension of the chain length by one carbon (i.e., substrate **12a**) led to a surprisingly good yield of the

Table 2. Scope of the Aminolactonization Reaction for the Formation of *gem*-Disubstituted Lactones[a]



entry	Ar	substrate	product	yield [%]
1		*o*- **10b**	**11b**	83
2		*m*- **10c**	**11c**	91
3		*p*- **10d**	**11d**	86
4		**10e**	**11e**	93
5		**10f**	**11f** 	72
6		**10g**	**11g**	79
7		X = O **10h**	**11h**	69
8		X = S **10i**	**11i**	64
9		**10j**	**11j**	62
10		**10k**	**11k**	77

[a] Reaction conditions: olefins (1.4 mmol), $NsNH_2$ (1.8 mmol), PhIO (1.8 mmol), $Cu(MeCN)_4PF_6$ (10 mol %), ligand **A** (12 mol %), MeCN, rt, 48 h under inert atmosphere with 4 Å molecular sieves.

δ-lactone **13a** (69%, Table 3, entry 1). Further elongation of the chain as in compound **12b**, however, provided only the intermediate aziridine **13b**, though in good yield (68%, entry 2). Replacement of the ester groups of **11a** and **12a** by an alcohol (**12c** and **12d**, respectively) furnished the corresponding tetrahydrofuran **13c** and dioxane **13d** in satisfying 66% and 67% yields (entries 3 and 4). Carbamates rather than esters can also be successfully used in this procedure, the *N*-Boc derivative **12e** providing the *gem*-disubstituted cyclic carbamate **13e** in 50% yield (entry 5). Finally, introduction of a stereogenic center on the substrate as in the amino acid derivative **12f** gave the highly substituted γ-lactone **13f** in 50% yield with a dr of 1.8:1 (entry 6).

The products obtained by this aminolactonization procedure can allow further elaboration to novel heterocyclic systems. Thus, as shown in Scheme 4, treatment of lactone **11f** with TFA in the presence of sodium acetate in dichloromethane gave the spiro lactone/lactam product **14** in

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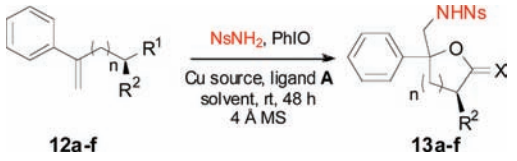
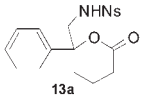
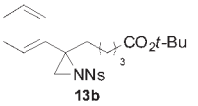
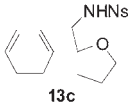
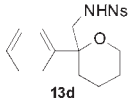
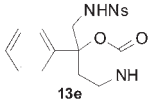
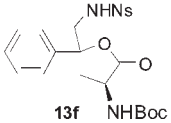
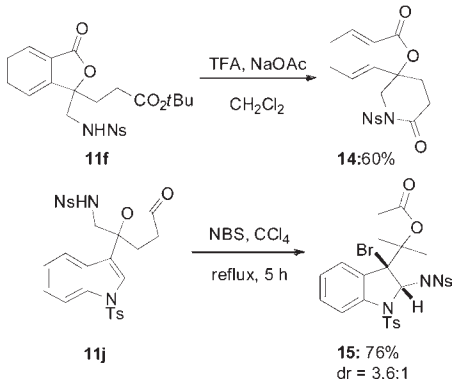
Table 3. Extension of the Aminolactonization Reaction for the Formation of *gem*-Disubstituted Heterocycles



entry		substrate	product	yield [%]
1	**12a**	$R^1 = CH_2CO_2tBu$ $R^2 = H$	 **13a**	69
2	**12b**	$R^1 = (CH_2)_2CO_2tBu$ $R^2 = H$	 **13b**	68
3	**12c**	$R^1 = CH_2OH$ $R^2 = H$	 **13c**	66
4	**12d**	$R^1 = (CH_2)_2OH$ $R^2 = H$	 **13d**	67
5	**12e**	$R^1 = NHBoc$ $R^2 = H$	 **13e**	50
6	**12f**	$R^1 = CO_2tBu$ $R^2 = NHBoc$	 **13f**	50 dr = 1.8:1

60% yield. Alternatively, reaction of the indole derivative **11j** with NBS led to formation of the hexahydropyrrolo-[2,3-*b*]indole spiro-lactone **15** in 76% yield (dr = 3.6:1). The hexahydropyrrolo[2,3-*b*]indole motif is present in a wide range of natural products and biologically active compounds,[11] and our method now allows easy access to

Scheme 4. Application of the Aminolactonization Reaction to the Synthesis of Novel Heterocyclic Systems



C-3 functionalized derivatives, very few of which have been described.

In conclusion, we have developed a new, high yielding aminolactonization procedure, analogous to the well-known halolactonization reaction, resulting from iminoiodane-mediated copper-catalyzed aziridination of styrene-derived 1-propanoates (or butanoates). The aminolactonization products can be further transformed into novel highly functionalized heterocyclic systems such as **14** and **15**. The full scope of this new reaction together with its application to the synthesis of natural products is currently in progress.

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Supporting Information Available. Experimental details, characterization data and spectra (^1H and ^{13}C NMR) for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.