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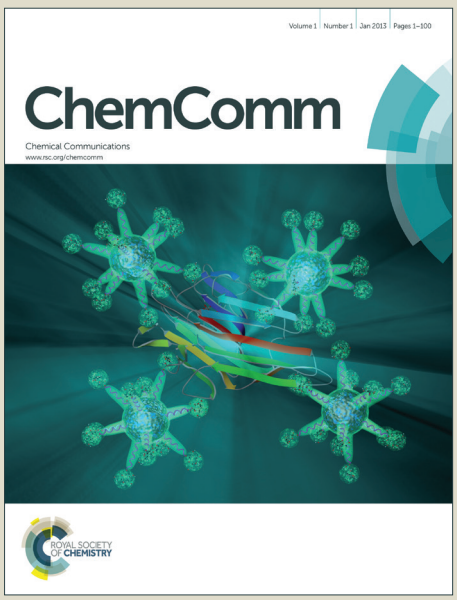

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Catalytic asymmetric aminolactonization of 1,2-disubstitued alkenoic acid esters: Efficient construction of aminolactones with all-carbon quaternary stereo-centre†

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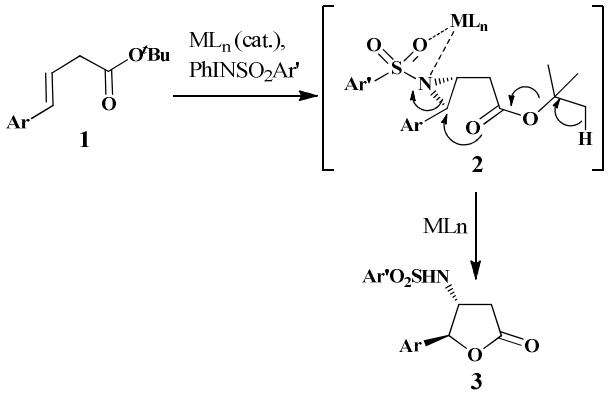
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Chiral BOX-Cu(OTf)$_2$ catalyzed enantioselective aminolactonization of *tert*-butyl ester of alkenoic acids has been developed via *in situ* aziridination using PhINNs as nitrene source. It provides exclusively *trans*-γ– and δ-amino lactones including additional all-carbon quaternary stereo-centre with up to 98% ee in good to excellent yields.

The oxidative intramolecular reaction of carboxylic acid and their derivatives with pendant olefins is an efficient tool for the construction of synthetically useful compounds like γ- and δ-lactones. Among the oxidative cyclization of alkenoic acids/derivatives, halolactonization is an age-old reaction that has widely been used in organic synthesis for the installation of remote chiral functionality.[1] Recently catalytic asymmetric halolactonization of prochiral alkenoic acids has progressed and matured enough with excellent diastereo- and enantioselectivity.[2] Asymmetric hydroxylactonization via epoxidation is also known in the literature and has proven to be a versatile transformation too.[3] However, synthetically useful, conceptually related asymmetric aminolactonization via aziridination has not yet been explored, though asymmetric aziridination[4] and subsequent ring opening reactions[5] are extensively studied. Our research interest towards asymmetric aminocyclization[6] via catalytic and enantioselective *in situ* aziridination, prompted us to investigate the aminolactonization of alkenoic acids/derivatives. Recently Dodd *et al* reported the aminolactonization of terminal alkenoic acid ester and one entry of non-racemic reaction with 48% of ee.[7] It was hypothesized that alkenoic acid esters **1** on aziridination would generate the aziridine **2** with a tethered carboxylic acid ester and γ-aryl substitution of the *in situ* generated aziridine may facilitate the *fused*-5-*endo*-cyclization to produce γ-lactones **3,** containing internal amino-functionality (Scheme 1). The aminolactones are valued enough to access several synthetic targets.[8-10] Herein we report the catalytic and enantioselective aminolactonization of internal β,γ– and γ,δ–alkenoic acid esters that provides γ– and δ–lactones, respectively, containing internal amino functionality with high diastereo- (dr >99:1) and enantio-selectivity (*ee* upto 94%) and also synthesis of aminolactones having all-carbon quaternary stereo-centre with excellent diastereo- (dr >99:1) and enantioselectivity (*ee* upto 98%).



Scheme 1 Proposed aminolactonization via aziridination

One of the more convenient ways for direct and stereoselective conversion of alkene to aziridine is by the action of iodinane ylides (ArI=NSO$_2$Ar) under copper catalyzed reaction conditions.[11] Recently, copper catalyzed iminoiodinane mediated stereoselective aminoarylation reactions have extensively been studied in our laboratory.[6] Cu(OTf)$_2$ was found to act as an efficient dual catalyst for aziridination and subsequent Friedel-Crafts cyclization reaction of the *in situ* generated aziridine and combination of the same with chiral bis-oxazoline (BOX) ligand led to high enantioinduction. In the allied studies PhINSO$_2$(4-NO$_2$C$_6$H$_4$) [PhINNs] was recognized as the better nitrene precursor than PhINSO$_2$(4-MeC$_6$H$_4$) [PhINTs]. It is also experienced that the PhINSO$_2$Ar species undergoes decomposition in the presence of carboxylic acid. So aminolactonization of alkenoic carboxylic acid via *in situ* aziridination was not successful. Accordingly *tert*-butyl ester of alkenoic acid is used where *tert*-butyl group serves to mask the carboxylic acid. It was assumed that chelation of the Lewis acid with *N*-nosyl moiety of aziridine would generate a partial positive charge on the benzylic carbon of the aziridine, which would facilitate the subsequent lactonization with the release of the *tert*-butyl group as butylene (Scheme 1). Thus *tert*-butyl ester of homocinnamic acid **1a** was reacted with PhINNs in the presence of BOX-Cu(OTf)$_2$ catalyst and showed an encouraging result (Table 1). It is to be noted that there was no reaction in the absence of BOX ligand.

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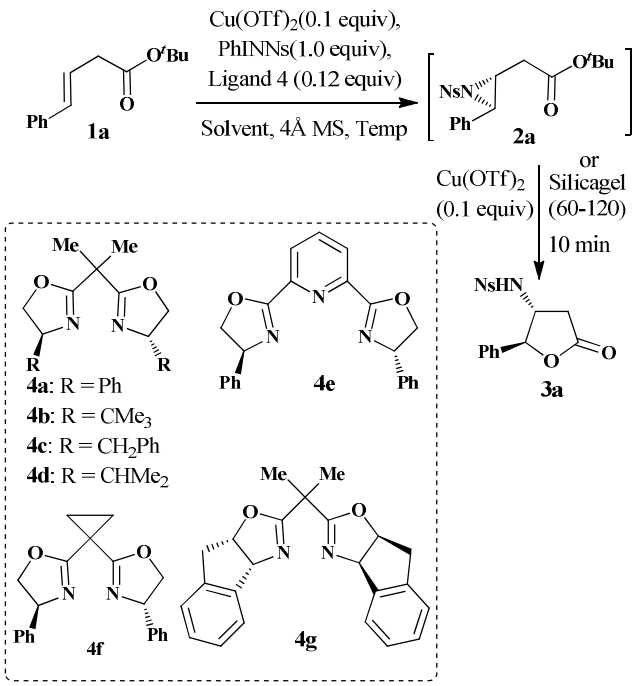
Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

† Dedicated with respect to Professor Ganesh Pandey on the occasion of his 60th birthday.

Table 1 Optimization of asymmetric aminolactonization of alkenoic acid ester **1a**.



Entry	Ligand	Solvent	T (°C)	*t* (h)	Yield[a] (%)	ee[b] (%)
1	**4a**	CH_2Cl_2	30	12	81	43[c]
2	**4b**	CH_2Cl_2	30	24	26	15[c]
3	**4c**	CH_2Cl_2	30	24	39	12[c]
4	**4d**	CH_2Cl_2	30	24	Trace	ND
5	**4e**	CH_2Cl_2	30	24	31	0
6	**4f**	CH_2Cl_2	30	24	44	0
7	**4g**	CH_2Cl_2	30	18	72	63
8	**4g**	$ClCH_2CH_2Cl$	30	24	64	41
9	**4g**	$CHCl_3$	30	24	68	90
10	**4g**	C_6H_6	30	24	15	53
11	**4g**	CH_3CN	30	18	70	21
12	**4g**	$CHCl_3$	40	20	80	87

[a] Isolated yield after flash column chromatography. [b] Enantiomeric excess was determined by HPLC. [c] The other enantiomer was predominantly formed. [d] ND = Not determined.

Reaction of **1a** (5.0 equiv) with PhINNs (1.0 equiv) was carried out in the presence of $Cu(OTf)_2$ (0.1 equiv) and phenyl-BOX ligand **4a** (0.12 equiv) derived from *L*-phenyl glycine in CH_2Cl_2 at 30 °C. After complete dissolution of PhINNs (12 h), the reaction mixture was treated with an additional amount of $Cu(OTf)_2$ (0.1 equiv). Within 10 min, the intermediate compound transformed to exclusively *trans*-aminolactone **3a** (dr >99:1) with 43% of *ee* in 81% of yield (Table 1; entry 1). Every attempt to isolate the intermediate aziridine **2a** by column chromatography failed; we always ended up with the cyclised product **3a**. The enantioselectivity (*ee*) and yield of the cyclized product 4-nosylamido-5-phenylbutyrolactone **3a** on silica gel was not affected. So we opted for the silica gel (60-120 mesh) mediated lactonization instead of additional $Cu(OTf)_2$.

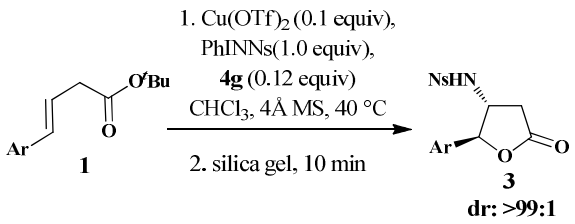
To optimize the yield and enantioselectivity, the reaction was studied with different BOX ligands in a variety of solvents and with variation of reaction temperature as well. For the reaction of **1a** in the presence of BOX ligands **4b-4d**, the dissolution of nitrene reagent was found to be incomplete even after 24 h and resulted in poor yields and *ee* (entries 2-4). Extra chelation due to Py-BOX ligand **4e** led to complete erosion of enantioselectivity (entry 5). Same result was also obtained for the phenyl BOX ligand **4f** with cyclo-propyl unit (entry 6). At last indanolamine derived BOX ligand **4g** was found to work well. The extra bulk of the indanolamine derived BOX ligand **4g**, compared to the phenyl BOX ligand **4a** may hinder the copper ion from obtaining good chelation, which is ultimately manifested in better enantioselevctivity (*ee* 63%; entry 7). The effect of solvent on this reaction was very substantial. In CH_2Cl_2, $ClCH_2CH_2Cl$, $CHCl_3$ and CH_3CN, yields were comparable but corresponding selectivities were quite decisive (entries 7-11). Chlorinated solvents resulted in comparatively higher chiral induction and $CHCl_3$ emerged as the best choice as solvent with *ee* of 90% under the same reaction conditions (entry 9).

The aziridination was also found to be very sensitive toward temperature. The reaction slowed down significantly on lowering the temperature and at 10 °C there was no reaction even after 48 h. When temperature was raised to 40 °C, yield increased to 80% from 68% with reduced enantioselectivity (87%), but pretty acceptable (entries 9 and 12). Both silica gel as well as additional amount of $Cu(OTf)_2$ facilitate the cyclization step. Enantioselectivity and yield in both cases were same. Thus the results are best explained by aziridine formation and cyclization, where the enantioselectivity originates in aziridination step which is carried over through lactonization step and there is no erosion of enantioselectivity. To support this further, instead of *tert*-butyl ester, the corresponding methyl ester was subjected to the reaction conditions in the presence of BOX ligand **4g** and the corresponding aziridine was isolated in 72% of ee. Lower ee of the aziridine from methyl alkenoic acid ester compared to amino lactone **3a** obtained from *tert*-butyl ester of alkenoic **1a** may be due to steric-demand.

Having set the optimized reaction condition, we explored the scope of this catalytic asymmetric aminolactonization reaction with a panel of substituted phenyl analogous substrates. For substrates **1b** and **1c** having halogen substituent at *para*- position of the aromatic ring, the reaction went through smoothly to provide the aminolactones **3b** and **3c** with very good *ee* of 90% and 86%, respectively (entries 2 and 3). Aziridination of *ortho*-substituted styrene is always a challenge. Substrate **1d** having *ortho*-chloro substituent afforded the highest *ee* of 94% (entry 4). *ortho- and meta*-bromo substrates **1e** and **1f** easily underwent the reaction and provided satisfactory yield with comparable enantioselectivities (entries 5 and 6). Very fast aziridination was observed for substrate **1g** containing *para*-electron donating substituent and the product aminolactone **3g** exhibits 77% of *ee* (entry 7). It is worth mentioning that for electron rich substrates silica gel or additional Lewis acid for lactonization was not necessary as it directly produced the desired aminolactone. Our attempt to control the reaction by lowering the temperature did not improve the result. At 20 °C, the yield was similar, but *ee* fell off to 58%. At 0 °C the reaction of **1g** was very slow with incomplete consumption of nitrenoid reagent even after 24 h and resulted in poor yield and *ee*. Substrate **1h** showed similar reactivity as of **1a** and provided high yields of aminolactone **3h** with good enantiolselectivity (entry 8). Like substrate **1g**, **1i** also underwent fast reaction and provided directly amino lactone **3i** with good yield and ee (entry 9). The absolute stereochemistry of the aminolactone **3** produced in the presence of indanolamine

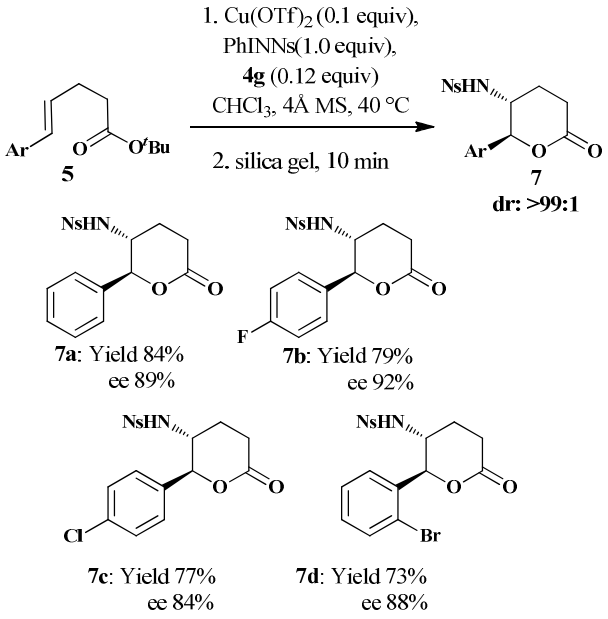
BOX ligand **4g** was assigned as (4*R*, 5*S*) by analogy with the literature reports.[6, 11]

Table 2 Generalisation of one pot aminolactonization reaction for β,γ–unsaturated carboxylic acid esters **1**.[a]



Entry	Ar	1	3	t^b (h)	Yield[c] (%)	ee[d] (%)
1	Ph	**1a**	**3a**	20	80	87
2	4-FC_6H_4	**1b**	**3b**	22	63	90
3	4-ClC_6H_4	**1c**	**3c**	24	68	86
4	2-ClC_6H_4	**1d**	**3d**	30	57	94
5	2-BrC_6H_4	**1e**	**3e**	30	56	80
6	3-BrC_6H_4	**1f**	**3f**	24	62	82
7	4-$MeOC_6H_4$	**1g**	**3g**	5 min	87	77
8	4-MeC_6H_4	**1h**	**3h**	20	83	88
9	3,4-$OCH_2OC_6H_4$	**1i**	**3i**	15 min	82	84

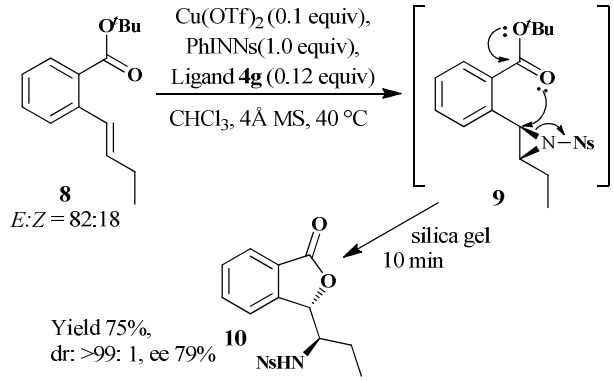
[a] Substrate **1** (5 equiv) and PhINNs (1.0 equiv) was employed BOX-Cu(II) complex, derived from 10 mol% $Cu(OTf)_2$ and 12 mol% BOX ligand **4g** in $CHCl_3$. The suspension was stirred at 40 °C. After dissolution of all the nitrenoid reagents, 0.2 g of silica gel (60-120 mesh) was added. [b] Total time including aziridine formation and subsequent lactonization. [c] Isolated yield after flash column chromatography. [d] Enantiomeric excess was determined by HPLC using chiralcel IA column.



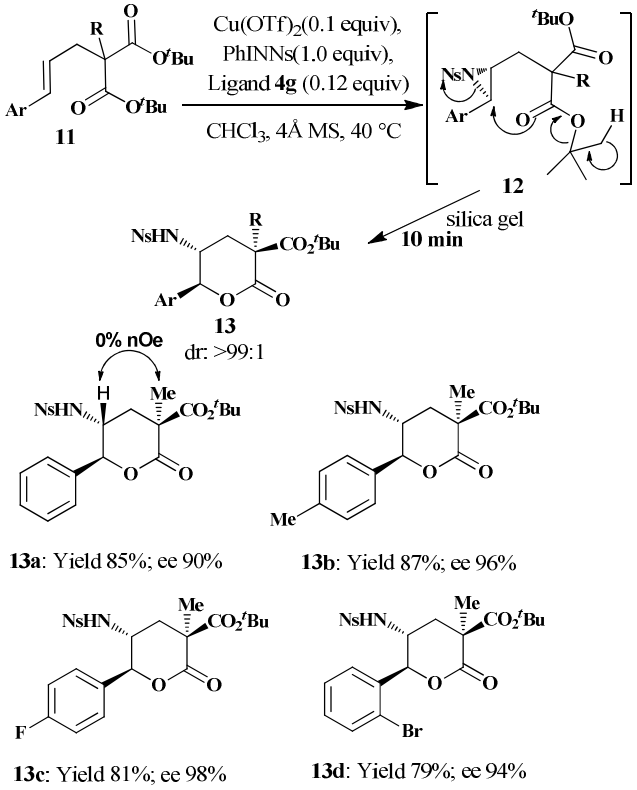
Scheme 2 One pot aminolactonization reaction of γ,δ–unsaturated ester **5**.

The novel aminolactonization reaction was also employed to higher homologous alkenoic acid esters **5** towards the synthesis of amino-δ-lactones **7**. Substrates **5a-d** reacted smoothly in the presence of indanolamine based BOX ligand **4g** under the same reaction conditions and afforded exclusively *trans*-products **6a-d** (dr>99:1) with high enantioselectivity and yields (Scheme 2).

The aminolactonization is also implemented to styrene **8**, where carboxylic ester functionality is tethered at *ortho*-position of arene moiety (Scheme 3). Substrate **8** (*E*:*Z* = 82:18) underwent smooth aminolactonization under the same reaction conditions *via spiro*-5-*exo*-*tet* ring opening of aziridine **9** and afforded exclusively lactone **10** with 79% *ee* in good yield.



Scheme 3 One pot aminolactonization reaction in *spiro*-5-*exo*-*tet* ring opening fashion

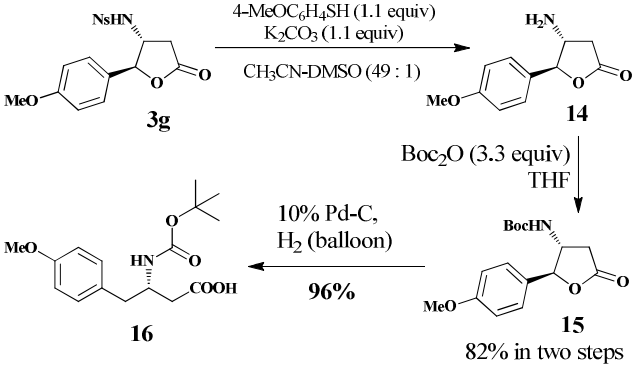


Scheme 4 Synthesis of δ-aminolactones with all-carbon quaternary stereo-centre

Asymmetric construction of all-carbon quaternary stereo-centre is of great interest and challenge to organic chemists.[12] This prompted us to investigate the aminolactonization of alkene having pro-chiral *gem*-dicarboxylic acid ester **11**. It was hypothesized that during lactonization one of the *tert*-butyl ester

moieties would be involved in stereoselective cyclization and lead to generation of all-carbon quaternary chiral centre. Thus substrate **11a** was reacted with PhINNs in the presence of $Cu(OTf)_2$-BOX **4g** catalyst under standard reaction conditions (Scheme 4). We are delighted to report that it exclusively provided only one isomer of amino-δ-lactone **12a** having all-carbon quaternary stereo-centre in high yield and enantioselectivity. This strategy is also generalized with few substrates **11b-11d**, which afforded excellent enantioselectivity (ee up to 98%) and yields (Scheme 4). Stereochemistry of the all-carbon quaternary centre is assigned by nOe experiment.

The aminolactones are important structural motifs that are present in or are precursors to many biologically important compounds.[8,9] For example, aminolactones **3** can easily be transformed to β-benzyl-β-amino acids (Scheme 5), which are the key precursors to many compounds.[9] As an application, aminolactone **3g** was converted to β-aminoacid by reductive lactone opening. However, Pd/C-catalyzed direct hydrogenation of **3g** to the corresponding *N*-nosyl-β-amino acid was not successful. So it was converted to *N*-Boc-aminolactone **15** on treatment with 4-methoxythiophenol and subsequent Boc-protection. Compound **15** on hydrogenation in the presence of Pd/C gave desire *N*-Boc-β-amino acid **16** in excellent yield. The optical rotation of **16** {$[\alpha]_D^{26}$ = -17.4 (*c* 1.1, EtOH)} was compared with the literature data[13] {$[\alpha]_D^{20}$ = -18.7 (*c* 1, EtOH)}, and the absolute stereochemistry of amino acid **16** was confirmed to be (*S*). In turn it further confirms the absolute stereochemistry of aminolactone **3** as (4*R*, 5*S*).



Scheme 5 Synthesis of *N*-Boc β-benzyl-β-amino acid **16**

In summary, we have developed an efficient enantioselective aminolactonization of internal alkenoic acid esters via *in situ* aziridination using chiral BOX-$Cu(OTf)_2$ catalyst. This report represents an elegant route to the formation of exclusively *trans*-γ- and δ-lactones containing amino-functionality with synthetically useful yields and enantioselectivities (ee up to 94%). Aminolactonization of olefin with tethered pro-chiral *gem*-diester efficiently afforded amino lactones with all-carbon quaternary stereo-centre in very high yields with excellent diastereo- (>99:1) and enantioselectivity (ee: 94 to 98%). Further application of the method is exemplified by transforming the amino γ-lactone **3** to *N*-Boc-β-benzyl-β-amino acid.

We thank DST, New Delhi for providing financial support. SMSA and SMA thank UGC and CSIR, New Delhi, respectively, for their fellowships. The authors are thankful to the referees for constructive scientific comments and suggestions.

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