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Bifunctional Reactivity of Cu^{I}: Sequential Ring Opening/N-Arylation

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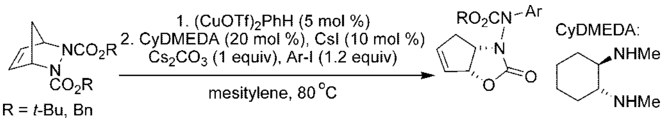
ABSTRACT

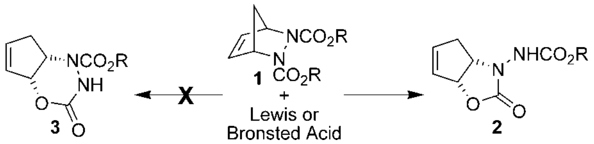


The sequential use of a single Cu^{I} catalyst enables the one-pot synthesis of *N'*-arylaminooxazolidinones through a Lewis acid catalyzed rearrangement followed by an *N*-arylation reaction. Contrary to previous reports, the formation of a *cis*-fused 5,5-membered ring system occurs during the rearrangement, as proven by X-ray crystallography.

The design and development of sequential processes using cheap and abundant metals is a valuable goal in modern catalysis. Low cost metals such as copper are particularly desirable, as several oxidation states are catalysts for both Lewis acid[1] and/or carbon−heteroatom bond-forming reactions.[2] Copper(I) complexes in particular are highly effective Lewis acids and catalysts for N-arylation/vinylation reactions. Herein we report a process that exploits the Lewis acid and N-arylation activity of Cu^{I} in a sequential manner, leading to the structural revision of the ring-opening products of bicyclic hydrazines.

Recent research into the transition metal catalyzed reactions of [2.2.1] bicyclic hydrazines by our group[3] and others[4] led us to investigate the intramolecular ring opening of this class of molecules. The intramolecular ring opening reported by Mackay and Micouin using Brønsted[5] and Lewis acids[4a] (Scheme 1) formed an interesting 5,6-membered heterocyclic ring system that we hoped to functionalize and form a variety of analogues.

Scheme 1



Through the screening of a variety of conditions, we found that several of catalytic Lewis acids could effect the intramolecular ring opening of bicyclic hydrazines **1a** and

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(1) See: (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335. (b) Sibi, M. P.; Cook, G. R. *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim , 1998; Vol. 2. (c) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, *322*, 1–3236.

(2) See: (a) Chemler, S. R.; Fuller, P. *Chem. Soc. Rev.* **2007**, *36*, 1153–1160. (b) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845–866. (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439. (d) Finet, J.-P.; Fedorov, A. Y.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, *6*, 597–626. (e) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.

(3) (a) Menard, F.; Lautens, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2085–2088. (b) Menard, F.; Weise, C. F.; Lautens, M. *Org. Lett.* **2007**, *9*, 5365–5367.

(4) (a) Pérez Luna, A.; Cesario, M.; Bonin, M.; Micouin, L. *Org. Lett.* **2003**, *5*, 4771–4774. (b) Sajisha, V. S.; Mohanlal, S.; Anas, S.; Radhakrishnan, K. V. *Tetrahedron* **2006**, *62*, 3997–4002. (d) John, J.; Sajisha, V. S.; Mohanlal, S.; Radhakrishnan, K. V. *Chem. Commun.* **2006**, 3510–3512. (e) Sajisha, V. S.; Radhakrishnan, K. V. *Adv. Synth. Catal.* **2006**, *348*, 924–930. (f) Anas, S.; Sajisha, V. S.; Mohanlal, S.; Radhakrishnan, K. V. *Synlett* **2006**, 2399–2402. (g) Storsberg, J.; Nandakumar, M. V.; Sankaranarayanan, S.; Kaufmann, D. E. *Adv. Synth. Catal.* **2001**, *343*, 177–180. (h) Yao, M.-L.; Adiwidjaja, G.; Kaufmann, D. E. *Angew. Chem., Int. Ed.* **2002**, *41*, 3375–3378.

(5) (a) Chung, C. Y.-J.; Mackay, D.; Sauer, T. D. *Can. J. Chem.* **1972**, *50*, 1568–1573. (b) Dao, L. H.; Mackay, D. *Can. J. Chem.* **1978**, *56*, 1724–1728. (c) Bournaud, C.; Robic, D.; Bonin, M.; Micouin, L. *J. Org. Chem.* **2005**, *70*, 3316–3317.

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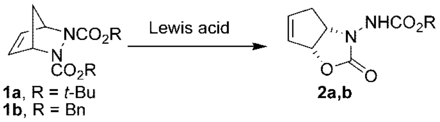
Table 1. Intramolecular Ring Opening of Bicyclic Hydrazines



entry	1	Lewis acid[a]	solvent	additive[b]	temp (°C)	yield (%)
1	**1a**	Cu(OTf)$_2$	THF		22	99
2	**1a**	Cu(OTf)$_2$	CH$_2$Cl$_2$		22	99
3	**1a**	(CuOTf)$_2$PhH	toluene		80	99
4	**1b**	Cu(OTf)$_2$	CH$_2$Cl$_2$		22	0
5	**1b**	Cu(OTf)$_2$	THF		22	*c*
6	**1b**	Cu(OTf)$_2$	THF	PhCO$_2$H	22	82
7	**1b**	(CuOTf)$_2$PhH	toluene	PhCO$_2$H	80	97
8	**1b**	(CuOTf)$_2$PhH	toluene		80	98

[a] 10 mol % based upon the metal. [b] 1 equiv. [c] Complete reaction, but polymerization of THF made product isolation difficult.

1b with particular focus on copper-based Lewis acids. (Table 1). We found that the Boc-protected bicycle **1a** underwent smooth ring opening with Cu(OTf)$_2$ and (CuOTf)$_2$PhH in a variety of solvents (entries 1−3).[6] When the analogous reaction was tried with Cbz-protected bicycle **1b** with Cu(OTf)$_2$, the reaction did not proceed in CH$_2$Cl$_2$ but went to completion in THF accompanied by polymerization of the solvent (entries 4 and 5), suggesting that a cationic species was being formed. The addition of a proton source such as benzoic acid enabled catalyst turnover and consumed the cationic byproduct (entry 6).[7] We next turned our focus to (CuOTf)$_2$PhH as a Lewis acid and found that at elevated temperatures it was equally effective. In toluene, the conversion of **1b** to **2b** proceeds in excellent yield without the addition of benzoic acid. Toluene is sufficiently nucleophilic to trap the carbocation byproduct[8] and acts as a proton source to turnover the catalyst through rearomatization.

Scheme 2. Proposed Mechanism of Ring Opening

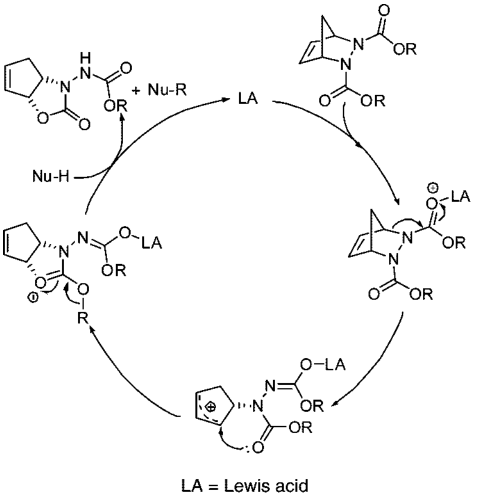
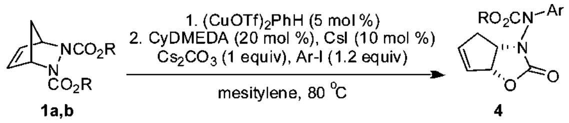
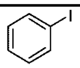
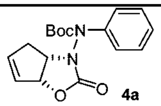
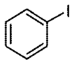
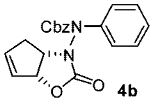
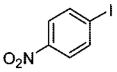
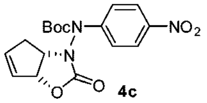
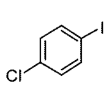
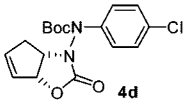
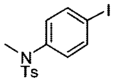
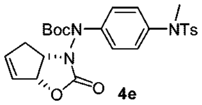
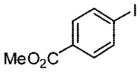
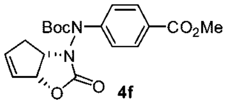
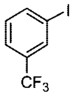
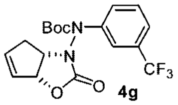
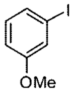
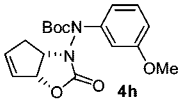
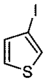
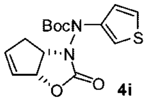


Table 2. One-Pot Ring Opening/N-Arylation



entry	1	Ar-I	product	yield (%)
1	**1a**		 **4a**	81
2	**1b**		 **4b**	48
3	**1a**		 **4c**	72
4	**1a**		 **4d**	66
5	**1a**		 **4e**	74
6	**1a**		 **4f**	72
7	**1a**		 **4g**	62
8	**1a**		 **4h**	66
9	**1a**		 **4i**	62

The ring-opening products **2a** and **2b** were viscous oils; however, through N-arylation (vide infra) we were able to obtain X-ray crystal structures that confirmed the structure of the products as the 5,5-*cis*-fused ring system.[9] This structure is different from the 5,6-*cis*-fused ring system (**3**) reported by Micouin in Brønsted and Lewis acid promoted ring openings of **1b**. We repeated the conditions reported by Micouin and found that Brønsted acid catalyzed,[5c] Lewis acid promoted,[4a] and our catalytic conditions all produced spectroscopically identical materials identified as **2b**.[9] From these results, we report a revised mechanism for the ring opening as depicted in Scheme 2, where the ring-forming step proceeds through a 5-*exo*-*trig* cyclization. It should be noted that the subsequent transformations reported by Micouin[5c] are not affected by the discrepancy in structure.

Our success with $\mathrm{Cu^I}$ as a ring-opening catalyst prompted us to explore the possiblility of generating *N*-aryl analogues of compounds **2a** and **2b** in one pot. There have been numerous recent reports of sequential $\mathrm{Cu^I}$-catalyzed heteroatom arylation or vinylation reactions,[10] but few if any reports that exploit both the Lewis acidity and carbon−heteroatom bond-forming ability of $\mathrm{Cu^I}$ species. During our optimization, we found that the desired sequence can be performed sequentially in one pot, as $\mathrm{Cu^I}$-diamine catalysts for N-arylation were not compatible with the ring-opening reaction. Through the screening of reaction parameters, we found the conditions outlined in Table 2 to be optimal, affording compound **4a** in 81% yield from **1a**. The addition of a catalytic amount of CsI, which presumably forms CuI in the reaction medium, increased the yields of product, although comparable yields were obtained in the absence of CsI.[11] Under our optimized conditions, compound **1b**, which undergoes clean conversion to **2b**, generally affords lower yields for the sequential N-arylation reaction.

We screened a variety of aryl iodides[12] as coupling partners with compound **1a** (Table 2, entries 3−9). Electron-deficient aryl iodides worked quite well; however, electron-rich aryl iodides (with electron-donating groups *para* to the iodide) afforded little to no desired product. In general, substitutents *ortho* to the iodide also failed to generate the desired products.

In summary, we have developed a one-pot method that sequentially exploits the Lewis acid and C−N bond-forming ability of $\mathrm{Cu^I}$. Our efforts enabled the synthesis of a variety of *N*′-arylaminooxazolidinones and proved the structure of the ring-opening products through X-ray crystallography. Our future efforts in this area will explore other coupling reactions that can be performed in one pot.

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

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(6) Cationic copper species with weakly coordinating counterions (TfO, $\mathrm{SbF_6}$, etc.) were necessary for effective catalysis of the ring opening reaction.

(7) Benzyl benzoate was isolated from the reaction mixture.

(8) A regioisomeric (*ortho*/*para*) mixture of diarylmethanes was isolated from the reaction mixture.

(9) See Supporting Information.

(10) See: (a) Chen, W.; Li, J.; Fang, D.; Feng, C.; Zhang, C. *Org. Lett.* **2008**, *10*, 4565–4568. (b) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 3535–3538. (c) Jiang, B.; Tian, H.; Huang, Z.-G.; Xu, M. *Org. Lett.* **2008**, *10*, 2737–2740. (d) Martín, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379–3382. (e) Rodríguez Rivero, M.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973–976.

(11) In the absence of added CsI, **4a** was obtained in 76% yield.

(12) Under the reaction conditions, aryl bromides afforded significantly lower yields, aryl chlorides afforded traces of product, and aryl triflates were unreactive.