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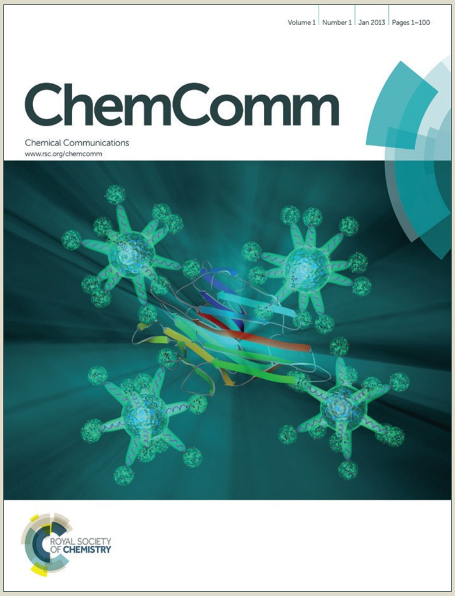

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Organoselenium and DMAP Co-Catalysis: Regioselective Synthesis of Medium-Sized Halolactones and Bromooxepanes from Unactivated Alkenes†

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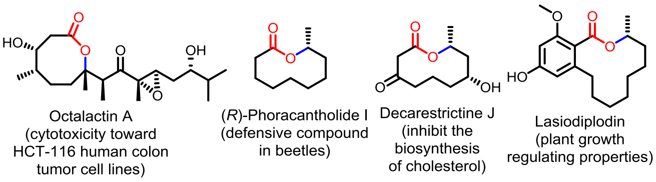
A catalytic system consisting of bis(4-methoxyphenyl)selenide and 4-(dimethylamino)pyridine (DMAP) has been developed for the regioselective synthesis of medium-sized bromo/iodo lactones and bromooxepanes possessing high transannular strain. ^{77}Se NMR, mass spectrometry and theoretical studies reveal that the reaction proceeds *via* quaternary selenium intermediate.

The applications of organoselenium reagents in the synthetic chemistry have been well-established, and being explored for various transformations.[1] Organoseleniums used as efficient catalysts for the oxidation, and electrophilic halogenation reactions of alkenes,[2,3] as selenium enhances the electrophilic nature of halogen.[3e]

Medium-sized lactones have attracted considerable interest to the researchers because of their difficulty in preparation, interesting biological activities and structural diversity.[4] In contrast to the synthesis of five and six membered halolactones,[5] synthetic protocols for the medium-sized halolactones, and oxepanes are rare, despite their potential applications in the synthesis of biologically important natural products (Fig 1).[6,7]



Octalactin A (cytotoxicity toward HCT-116 human colon tumor cell lines)

(*R*)-Phoracantholide I (defensive compound in beetles)

Decarestrictine J (inhibit the biosynthesis of cholesterol)

Lasiodiplodin (plant growth regulating properties)

Fig 1. Biologically important medium-sized lactones

The substrate with long alkyl chain possesses high degree of conformational flexibility that brings a negative entropy change in the intramolecular cyclization process,[8b] also transannular strain is one of the dominant factors which increases the enthalpy of activation in the formation of medium-sized lactones.[8] High thermodynamic barrier diminishes the formation of seven to nine-membered lactones by 10^4 to 10^6 times than that of six-membered analogues.[8b,12a] Synthesis of medium-sized lactones has been achieved under dilution conditions, slow addition of reagents,[9] using TM-catalysts,[10] and bifunctional substrates.[11] Rousseau *et al.* described the synthesis of iodolactones and iodooxepanes using highly activated iodine source [bis(sym-collidine)iodine(I)]$^+$PF$_6^-$ under slow addition conditions.[12] Lewis acid-mediated ring expansion by the cycloaddition of alkyne to the *in-situ* generated oxetenium species was also applied for the construction of medium-sized lactones.[13] Recently, Yeung *et al.*, have given a representative procedure for the synthesis of bromolactones using sulfur-based zwitterion catalyst.[14a] The report describes the synthesis of only one seven-membered bromolactone from alkyl chain substrates and higher size lactones were achieved by the incorporation of the heteroatom, which lowers the transannular strain in the chain. Moreover, cyclization of alkenols for the synthesis of medium-sized bromooxepanes has not been accomplished under catalytic conditions. In continuation of our work on organoselenium chemistry,[15] and synthesis of heterocyclic compounds,[16] herein we disclose a new method for the regio- and stereo-selective construction of medium-sized bromo, iodolactones, and bromooxepanes by using organoselenium catalyst, DMAP co-catalyst and NBS/NIS as a halogenating reagent and crystal structure study of several medium-sized lactones has been reported for the first time.

Optimization of reaction conditions were carried out on the 6-heptenoic acid substrate by screening various organoselenides **1a-1g**, co-catalysts **2a-2e**, brominating reagents, additives, and solvents (Scheme 1 and detailed study is presented in the Table S1, ESI page S3-S5). Noteworthy, selenide **1e** alone failed to provide bromolactone **3**, and also DMAP provided poor yield of **3** from 6-heptenoic acid, and NBS. However, catalyst **1e** together with co-catalyst DMAP gave **3** in 64% yield. After extensive screening of various conditions, we have chosen catalyst **1e** (10 mol %), co-catalyst **2a** (20 mol %), NaHCO$_3$ (1

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† Experimental details, spectroscopic data, ^{1}H, ^{13}C, 135-DEPT, ^{77}Se, 2D-NMR, mass spectra and X-ray crystallographic data [CCDC No. 984340 (**1e**), 984339 (**3**), 1407583 (**18**), 984338 (**33**), 984341 (**1eb**)]. See DOI: 10.1039/x0xx00000x

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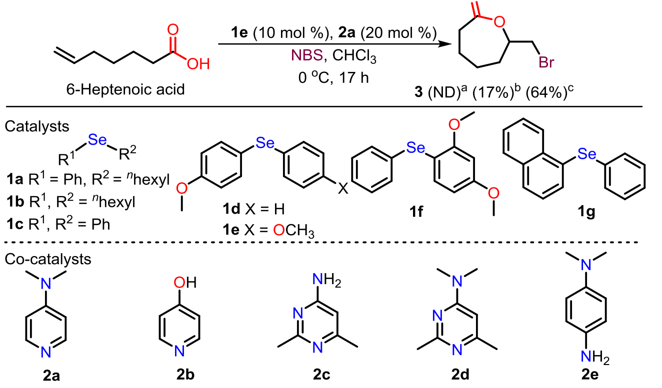
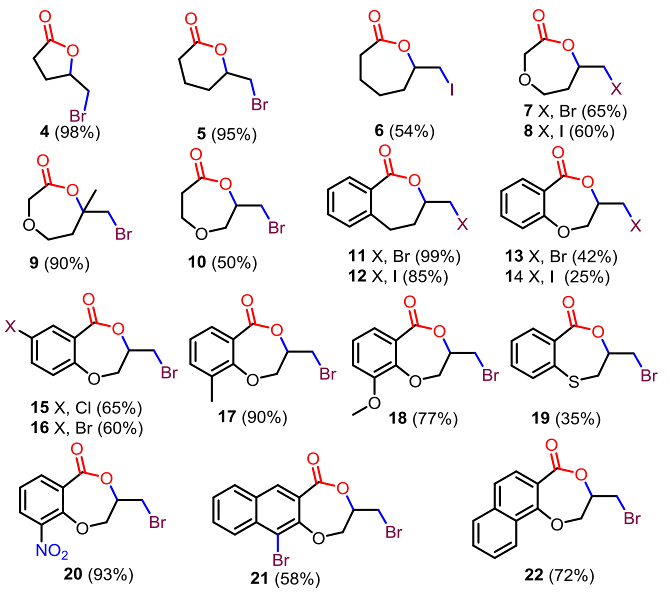
equiv), and NBS (2 equiv) in chloroform at 0 °C to explore further substrate scope of the reaction, and results are summarized in Scheme 2.



Scheme 1. Various catalysts and co-catalysts screened. ^{a,b,c} Yields obtained using **1e**, **2a**, and (**1e**+**2a**), respectively.



Scheme 2. Synthesis of seven-membered halolactones.

In the beginning, we have studied catalytic system for the synthesis of small-sized bromolactones. Indeed, quantitative yields of five- and six-membered bromolactones **4** and **5** were obtained under developed catalytic system. Next, synthesis of various seven-membered bromolactones **6**-**22** (Scheme 2) was explored from respective alkenoic acids. Bromolactones **7**-**10** having an oxygen heteroatom in the chain were obtained precedently in good (65-90%) yields, as heteroatom reduces the transannular strain and also stabilizes bromiranium ion in transition state by nonbonded intermolecular interaction.[12b] Bromolactone **11** consisting phenyl supported chain was isolated in quantitative yield (99%) within 3 h. Medium-sized lactone **13** containing phenyl as well as the heteroatom in the chain was obtained in moderate yields. Substitution on benzene ring, enhanced the yield of bromolactones (**15-18**, **20-22**). To our delight, medium-sized bromolactones **3**, and **18** were isolated as crystalline solids, which were reported as semisolids or liquids earlier.[12,14a] The crystal structures of lactones **3** and **18** are depicted in Fig 2 (for details see ESI page S50-S61).

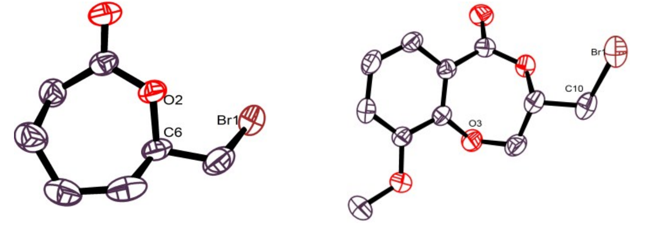
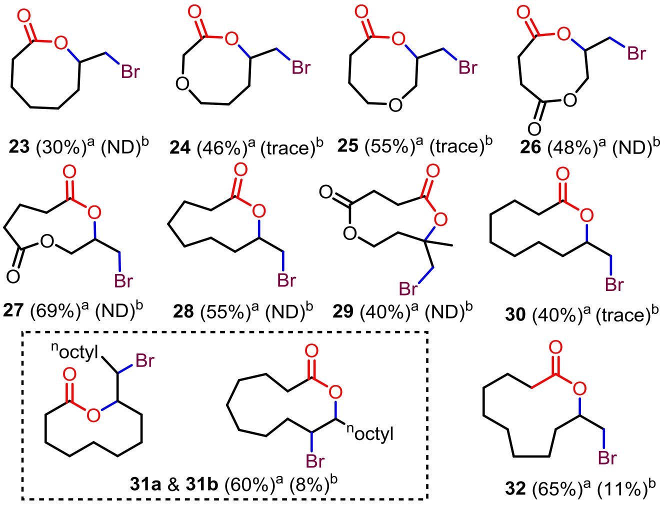


Fig 2. Crystal structures of bromolactones **3** and **18**, respectively with 50% ellipsoidal probability and hydrogen atoms are omitted for clarity.

Iodolactonization of selected alkenoic acids was also explored. Indeed the use of *N*-iodosuccinimide under optimized conditions, provided iodolactones **6**, **8**, **12**, and **14** in 25-85% yields.



Scheme 3. Synthesis of eight to eleven-membered bromolactones. ^{a,b}Yields obtained using (**1e**+**2a**), and **2a** (10 mol %), respectively.

Next, eight and higher-membered bromolactones were explored (Scheme 3). Synthesis of eight and higher-membered bromolactones has not been accomplished till date presumably due to high transannular strain; whereas only halolactones consisting of heteroatom such as oxygen, which reduces the strain have been reported. Alkenoic acid consisting only carbon atom in the chain provided novel eight-membered bromolactone **23** in 30% yield. Incorporation of the heteroatom in the alkyl chain provided improved yields (46-55%) of eight-membered bromolactones **24**-**26**. Nine-membered bromolactone **27** having oxygen as heteroatom in the ring was obtained as *exo*-isomer exclusively; on the other hand bromolactone **28** lacking oxygen atom formed *exo*-isomer as a major product and *endo*-isomer as minor product.[12c] 10- and 11-Membered bromolactones **29**, **30** and **32** were also obtained via *exo-trig* ring closure in 40-65% yields. Phoracantholide I (Fig 1) is a natural product consisting of 10-membered lactone moiety with defensive property in beetles. Here, bromo-derivative **30** of phoracantholide I was synthesized in 40% yield from 9-decenoic acid. Oleic acid having long alkyl chain provided both isomers **31a** and **31b** in 1:1 ratio. Synthesis of bromolactones **23**-**32** was also studied in the presence of DMAP **2a** alone, which failed to provide

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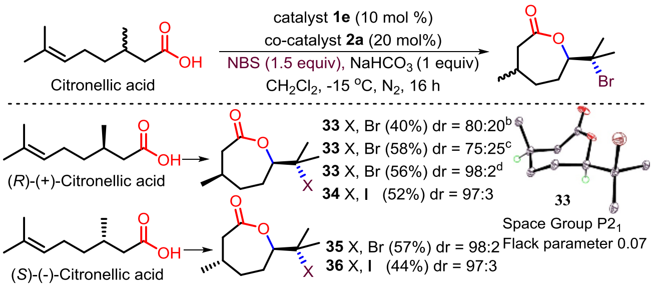
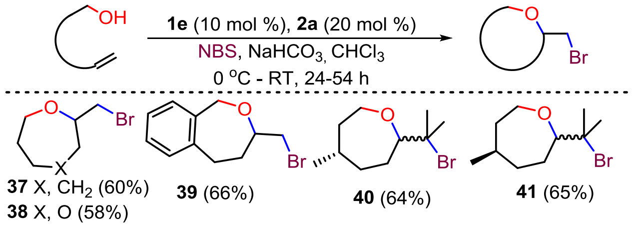
bromolactones **23**-**30**, although, 10- and 11-membered lactones **31** and **32** were obtained in poor yields 8 and 11% respectively.

Next, diastereoselectivity was examined in the halolactonization using selenide **1e** and **2a** catalytic system (Scheme 4). Indeed, (*R*)-(+)-citronellic acid gave bromolactone **33** diastereoselectively (98:2) under the reaction conditions. Worth noting, bromolactone **33** was obtained with poor diastereoselectivity (80:20) when only **2a** was used as a catalyst. Similarly, (*S*)-(-)-citronellic acid also gave diastereoselective bromolctone **35** (98:2). Iodolactonization in (*R*)-(+)- and (*S*)-(-)-citronellic acids also offered excellent diastereoselectivity for the synthesis of seven-membered iodolactones **34** and **36**. It seems that the formation of diastereoselective product was driven by dimethyl substituted carbon and an interaction with the catalytic intermediate (for details, see ESI page S8). Stereochemistry was also confirmed by the single crystal X-ray analysis of the bromolactone **33**.[17]



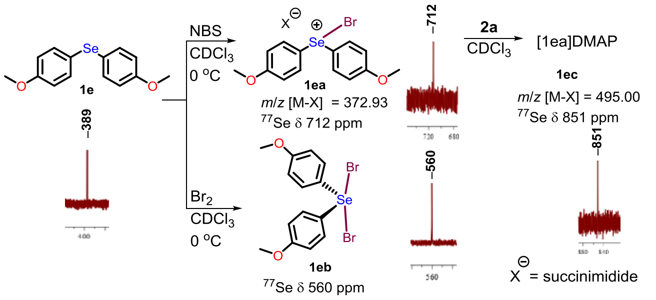
Scheme 4. Diastereoselective synthesis of halolactones. ^{a} Diastereomeric ratio determined by ^{1}H NMR; ^{b} DMAP alone used as a catalyst; ^{c} CHCl$_3$ was used as a solvent; ^{d} CH$_2$Cl$_2$ was used as a solvent.

With the optimized condition in hand, cyclo-bromoetherification reaction of alkenols was studied for the synthesis of seven-membered bromooxepanes (Scheme 5). Alkenols underwent bromoetherification reaction smoothly leading to various seven-membered bromooxepanes **37**-**39** in 58-66% yields. However, bromoetherification required considerably longer time (24-54 h) compared to the bromolactonization and could be due to slower deprotonation of alcohol than the acid (*vide infra*).[18] Bromooxepanes **40** and **41** were obtained with 64 and 65% yields as a racemic mixture of both diastereomers.



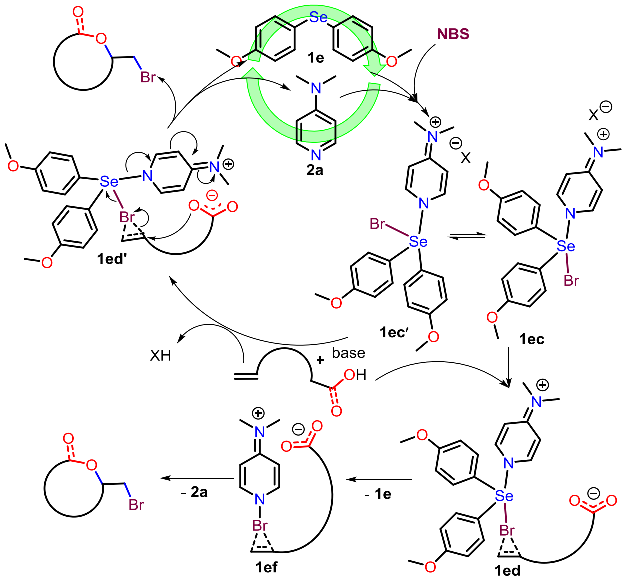
Scheme 5. Synthesis of bromooxepanes.

^{77}Se NMR, mass spectrometry and theoretical calculations were carried out to understand the co-operative effect of selenide **1d** and **1e** with co-catalyst **2a** in the bromolactonization reaction (for details, see ESI, page S6-S7). The reaction mixture of NBS and catalyst **1e** showed a peak at δ 712 ppm, attributed to **1ea** (Scheme 6), which is significantly downfield shifted as compared to selenide **1e** (δ = 389 ppm). The addition of co-catalyst **2a** to **1ea** leads to further downfield shift of the signal from δ 712 to δ 851 ppm and seems to be hypervalent Se(IV) **1ec** which could be in the equilibrium with **1ec'** (Scheme 7) as the calculated energy difference between **1ec** and **1ec'** is low (10 kcal/mol) and also the interconversion energy for both isomer is found to be 14.86 kcal/mol.[19]



Scheme 6. Mechanistic study by ^{77}Se NMR and mass analysis.

^{77}Se NMR study on the equimolar reaction mixture of selenide **1e**, DMAP **2a**, NBS and 6-heptenoic acid after 6 h, showed two peaks for **1e** (δ = 387 ppm) and **1ec** (δ = 851 ppm) (ESI page S346). Attempted isolation of **1ea** and **1ec** were unsuccessful and instead, Se(IV)Br$_2$ **1eb** was isolated. Selenium(IV) dibromide **1eb** alone and also with DMAP provided trace amount of **3** under optimized reaction conditions. The catalytic cycle for the construction of medium-sized bromolactones is depicted in Scheme 7.



Scheme 7. Proposed catalytic cycle for bromolactonization.

The reaction between **1e**, **2a**, and NBS provided intermediate **1ec** which may be in equilibrium with **1ec'**. Alkene and acid terminals of alkenoic acid would bind with the intermediate **1ec'** and give **1ed'**. Selenium-nitrogen coordination elongates the Se–Br bond[20] and thus favours the facile generation of Br$^+$. The formation of bromiranium ion and interaction of carboxylate ion with the ammonium ion in the same species would favour the cyclization that lead to medium-sized

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bromolactone **3** and concomitant regeneration of catalyst **1e** and co-catalyst **2a**.

In an alternative pathway, reaction of alkenoic acid with **1ec** provide the intermediate **1ed** which transfer the bromine to alkene and convert into **1ef** and release the selenide **1e**. Nucleophilic attack of oxygen to bromiranium ion, would give corresponding bromolactone.

In summary, we have presented a catalytic system for the efficient synthesis of medium-sized bromolactones and bromooxepanes from alkenoic acids and alkenols, respectively. The presented methodology is competitive with respect to the earlier developed methods and also provided access to several highly strained bromolactones, without the incorporation of heteroatoms. Asymmetric synthesis of the medium-sized bromolactones is currently under study in our laboratory.

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