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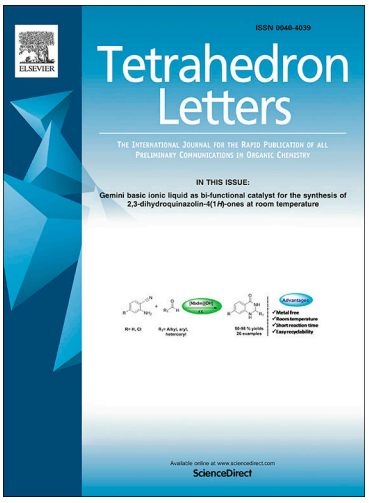

Enantioselective Bromolactonization of Aryl Functionalized Alkenoic Acids

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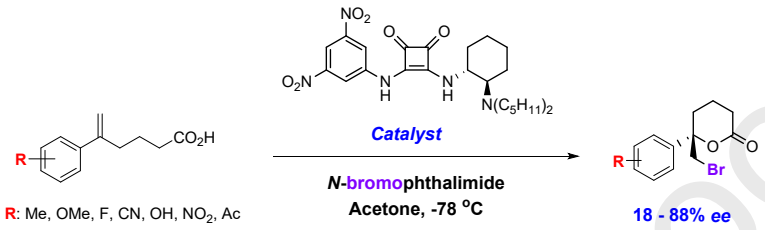

R: Me, OMe, F, CN, OH, NO_2, Ac

18 - 88% *ee*

Enantioselective Bromolactonization of Aryl Functionalized Alkenoic Acids

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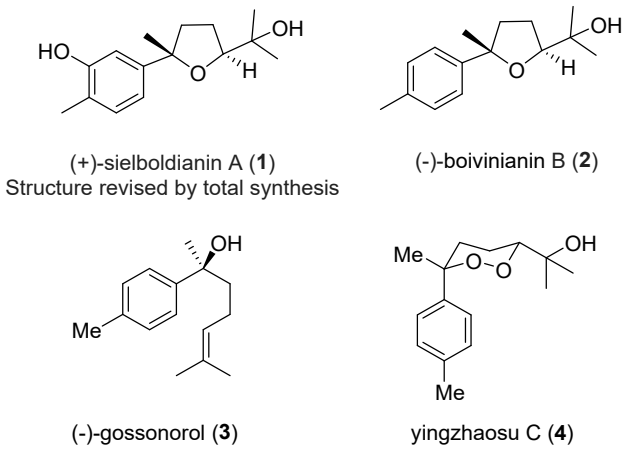
Abstract:
Aryl substituted 1,1-disubstituted alkenoic carboxylic acids were subjected to an enantioselective organocatalyzed protocol, yielding the corresponding δ-bromolactones in a regioselective manner. The products were isolated in good to high yields with enantiomeric excess in the range of 18 to 88%.

Keywords: Bromolactonization, enantioselectivity, δ-bromolactones, organocatalysis, chiral squaramide, H-bonding catalysis.

The electrophilic addition of halogens to alkenes is a classical synthetic reaction[1] with several advances recently reported affording a plethora of synthetically useful intermediates and products.[2,3] Among these electrophilic addition reactions, the halolactonization reaction has been used in the total synthesis of various natural products.[3b,4] The first catalytic enantioselective bromolactonization of alkenoic acids was presented in 2010 by Fujioka and co-workers,[5] and additional reports continue to be presented.[6]

In connection with our interest in developing enantioselective bromo- and iodolactonization protocols,[7] we found that squaramides with H-bonding properties with a chiral tertiary amine attached, provided high enantioinduction of the desired δ-halolactones. Of note, using our bromolactonization protocol with a limited selection of aryl-alkenoic acids under organocatalysis, enabled the stereoselective total synthesis of the sesquiterpenoids (+)-sielboldianin A (**1**), (-)-boivinianin B (**2**) and (-)-gossonorol (**3**), as well as a formal synthesis of yingzhaosu C (**4**) (Fig. 1).[7b,d]



(+)-sielboldianin A (**1**)
Structure revised by total synthesis

(-)-boivinianin B (**2**)

(-)-gossonorol (**3**)

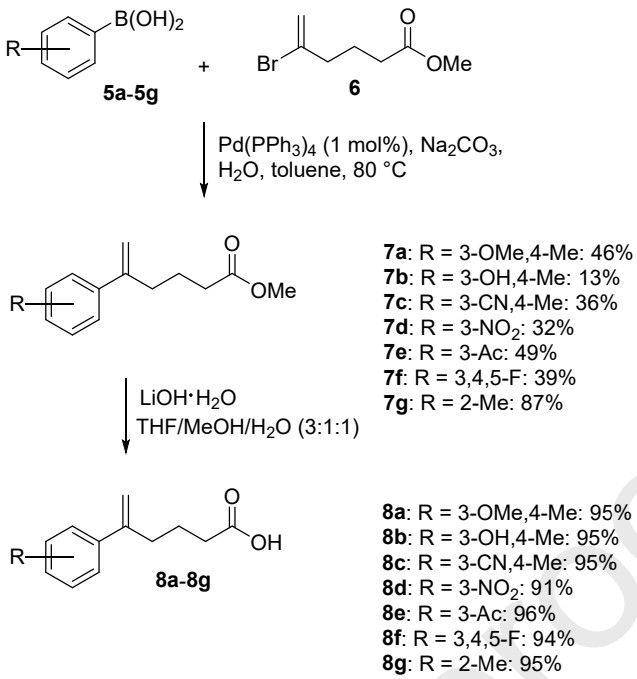
yingzhaosu C (**4**)

Figure 1. Examples of sesquiterpenoids prepared utilizing enantioselective squaramide catalyzed bromolactonizations.

Of interest, on both occasions,[7b,d] the organocatalyzed protocol was performed on multi-gram scale showing its practicality in the total synthesis of **1**-**3**. The greater chemical stability of the C-Br bond relative to the C-I bond[8] provides many advantages when using chiral bromolactones compared to their iodo-congeners, such as increased chemical stability, ease of purification often by recrystallization, as well as long-term storage. The utility of enantioselective halolactonization protocols in the total synthesis of natural products has also been demonstrated by other groups.[9,10] Murai, Fujioka and co-workers used a trisimidazoline catalyzed bromolactonization protocol in their synthesis of (-)-tanikolide, a metabolite of the cyanobacterium *Lyngbya majuscule*.[9] Martin and Klosowski successfully implemented their method for organocatalyzed asymmetric iodolactonization in a total synthesis of (+)-disparlure, constituting the shortest catalytic, enantioselective synthesis of this interesting insect pheromone.[10] Yeung and co-workers prepared a short synthesis of (+)-boivinianin A based on a regio- and enantioselective organocatalyzed bromolactonization.[11]

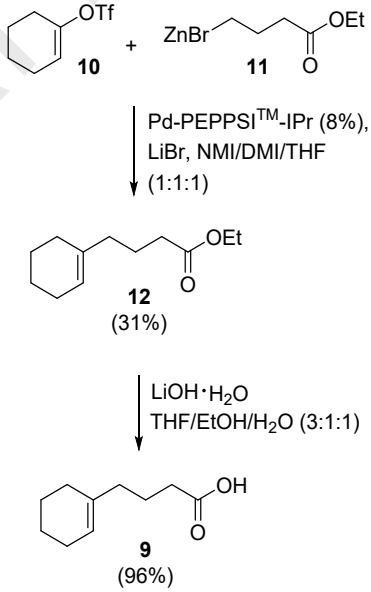
The importance of stereoselective total synthesis for the structural elucidation of natural products is well established.[12] The development of organocatalysis for the preparation of natural products is of current interest,[13] due to the lack of sensitivity to moisture and oxygen as well as the typically low toxicity of organocatalysts.[14] An extension of the substrate scope for our previously reported protocol is presented.

The different aryl substituted alkenoic acids were mainly obtained by using the Suzuki reaction[15] with aryl boronic acid **5a**-**5g** and vinyl bromide **6** to yield methyl esters **7a**-**7g**. Basic hydrolysis of **7a**-**7g** gave the corresponding carboxylic acids **8a**-**8g** (Scheme 1).



Scheme 1. Synthesis of substrates **8a-8g**.

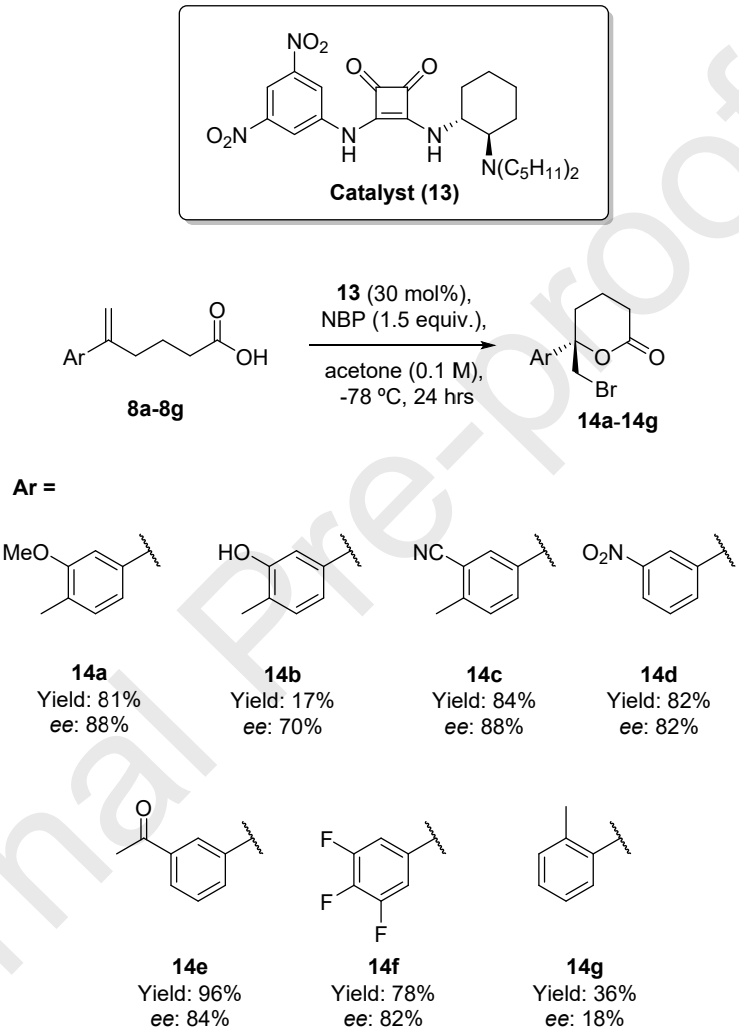
Substrate **9** was prepared by a Negishi reaction[16] between triflate **10** and commercially available zinc bromide **11** to produce **12** that was hydrolyzed to **9** (Scheme 2).



Scheme 2. Synthesis of substrate **9**.

Alkenoic acids not previously investigated in our protocol and carrying functionalities amendable for further synthetic transformations were chosen, see Scheme 3. Catalyst **13** has

proven superior among those studied.[7b,d] In the presence of 1.5 equivalents of *N*-bromophthalimide (NBP) in acetone (0.1 M) at -78 ºC, the desired products **14a**-**14g** were all formed regioselectively. For all products the *S*-configuration was assigned based on comparison of the specific optical rotation values reported in the literature[5] and by analogy with our earlier published protocol.[7b,7d] In the absence of the chiral catalyst **13**, the reaction time is 24-48 hours and yields only racemic products.[7e]

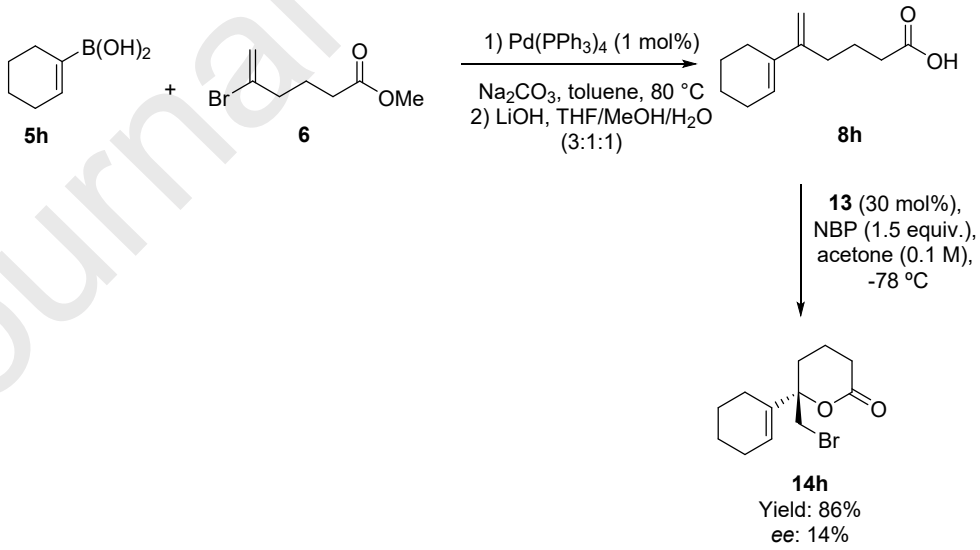


Scheme 3. Squaramide catalyzed enantioselective bromolactonization of alkenoic acids **8a-8g**.

Notably, using substrates with electron-donating groups in the *meta*-positions yielded the corresponding bromolactones in fairly high enantioselectivities (70 and 88% *ee*, **14a** and **14b**, respectively, Scheme 3). For aryl substituents with dual π-donors and σ-withdrawers in the *meta*-position, good enantioselective induction was expected, in light of the net reduced electron density in the 1,1-disubstituted alkene moiety. Indeed, enantioselectivities of 70 and 88% *ee* were obtained for **14a** and **14b** (Scheme 3). This stands in sharp contrast to our

previous reports of using a methoxy-group in the *para*-position, which results in only 9% *ee* of the ensuing bromolactone.[7b]

Aryl alkenoic acids with electron-withdrawing groups in the *meta*-position were well tolerated in this protocol, affording the bromolactone products **14c**-**14e** in both high yields (82-96%) and good enantioselectivities (82-88% *ee*), Scheme 3. Of interest, the nitrile, nitro and acetyl functionalities may all be utilized for further synthetic transformations by nucleophilic addition or by reduction. Investigation of substrates with an *ortho*-substituent was of interest as this has not been previously examined.[7b] Consequently, an *ortho*-tolyl alkenoic acid was then subjected to the established method, but unfortunately this afforded the bromolactone **14g** in only 18% *ee* and 36% yield. In comparison to the *para*-tolyl substrate (79% *ee*, 91% yield),[7b] *ortho*-substituents are seemingly not well tolerated in this protocol. When the aryl group of the alkenoic acid was replaced with a cyclohexene substituent in conjugation with the 1,1-disubstituted alkene moiety, the enantioselectivity was severely reduced (14% *ee*, 86% yield, **14h**, Scheme 4). The *S*-configuration was also assigned to **14h** using specific rotation values and by comparison with the literature.[5] Previously, it has also been demonstrated that aliphatic substrates with an *iso*-propyl or a cyclohexyl substituent on the alkene, result in poor enantiomeric excess of the products using this method (24 and 21% *ee*, respectively).[7b]



Scheme 4. Synthesis and squaramide catalyzed enantioselective bromolactonization of alkenoic acid **8h**.

In summary, an extension of the alkenoic acids investigated in our organocatalyzed enantioselective bromolactonization protocol has been presented. Such efforts are in demand for advancing the use of organocatalyzed enantioselective bromolactonization reactions in natural product total synthesis. As previously, only δ-bromolactones were obtained, further supporting the excellent regioselectivity earlier reported. The enantiomeric excess of the products formed from aryl functionalized 1,1-disubstituted alkenoic acids, were determined to be in the range of 18-88% *ee*. The two alkenoic acids **8h** and **9** with aliphatic substituents gave products **14h** and **15**, respectively, with low enantiomeric excess of 14 and 38% *ee*, respectively.

Acknowledgment

The Norwegian Research Council is gratefully acknowledged for funding of a doctoral fellowship to R. K. (FRIPRO-FRINATEK 230470).

Supplementary data

Supplementary data include experimental procedures and characterization data, copies of ^{1}H- and ^{13}C-NMR spectra, as well as copies of chromatograms of HPLC analyses.

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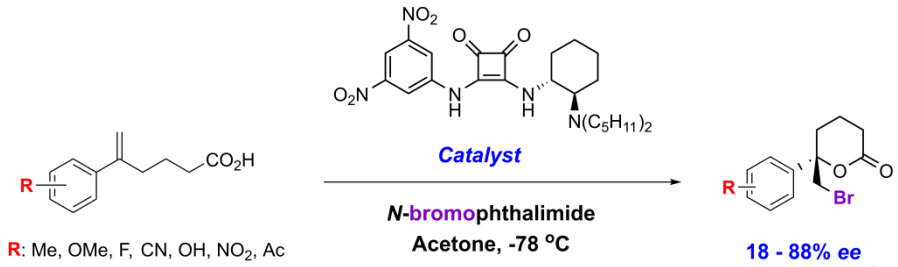

Highlights:

- An extension of an organocatalyzed bromolactonization protocol is presented
- Several aryl substituted 1,1-disbustituted alkenoic carboxylic acids were investigated
- The protocol is regioselective and the products were isolated in good to high chemical yields
- The enantioselectivity varied and depended on the substitution on the aryl ring

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: