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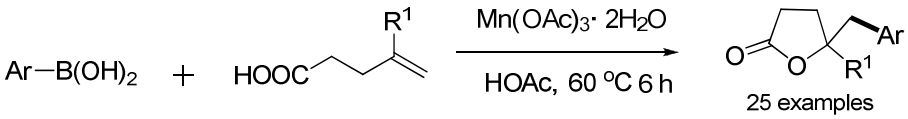

The general method for the synthesis of γ, γ-disubstituted butyrolactones via an arylation–lactonization of alkenoic acids process has been developed.

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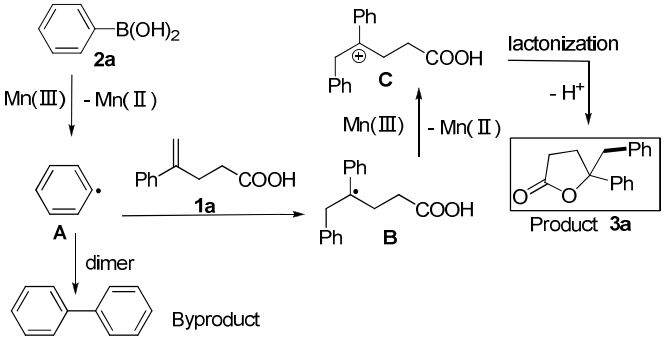
The general method for the oxidative cyclization of 4-alkenoic acids with arylboronic acids has been developed. The reactions described provide a novel access to γ, γ-disubstituted butyrolactones in moderate yields, allow the direct formation of a C-C bond and the construction of a lactone ring in one reaction.

γ-Butyrolactones as a class of readily available compounds are pervasive in nature. Owing to their interesting biological activities, the γ,γ-disubstituted butyrolactones have received much attention.[1] Consequently, the increasing demand for γ-butyrolactones has generated considerable interest in the development of efficient and flexible synthetic methods. In this context, classic methods for the synthesis of γ-butyrolactones including Baeyer-Villiger reaction of aryl cyclobutanones,[2] arylation of unsaturated lactones,[3] radical processes[4] or the inter/intra-molecular reactions of alkenes with nucleophiles.[5] Recently, difunctionalization of alkenes have provided a powerful strategy for the synthesis of various organic compounds, among which the carbolactonization of pent-4-enoic acids has been proved to be an efficient approach to benzyl-containing γ-lactones.[6] Fagnoni's group reported a first ultraviolet light-induced synthesis of benzyl- and aryl-substituted γ-lactone from phenyl halides used as precursors of the cations, wherein only electron-donating substituted phenyl halides could give satisfactory yields.[6a] In 2010, the Zhang's group developed the carbolactonization of terminal alkenes via oxidative gold catalysis, which showed that the alkylgold intermediates could be readily functionalized by arylboronic acids in the precense of excess Selectfluor.[6b]

However, these pioneering works are difficult to be used in the synthesis of γ,γ-disubstituted butyrolactones. In 2014, Xiao's group developed a visible light photocatalytic arylation–lactonization cascade of 4-alkenoic acids with aryldiazonium salts. Xiao's method provides a rapid and straightforward access to various γ, γ-disubstituted butyrolactones under very mild conditions.[6c] However, the high reactivity of aryldiazonium salts and hazardous profile make them unsuitable for safe handling, especially on a large scale.

Arylboronic acids represent versatile building blocks in organic synthesis. More recently, the aryl radical generated from arylboronic acid in the presence of some oxidants have been identified as coupling partners in the formation of carbon–carbon bonds.[7] Inspired by these results, we reasoned that generating directly the radical **B** by addition of phenyl radical **A** onto an olefin-acid would produce cationic intermediates through single-electron oxidation which ultimately afford γ, γ-disubstituted butyrolactone via a facile intramolecular nucleophilic addition. This transformation allows the direct formation of a C-C bond and the construction of a lactone ring in one reaction (Scheme 1).

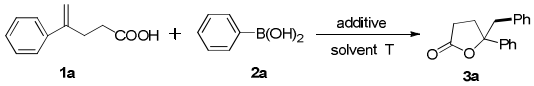


Scheme 1. Possible pathways in the reaction between aryl radical and unsaturated acid.

This idea was first examined by using 4-phenylpent-4-enoic acid (**1a**) and phenylboronic acid (**2a**) as reaction partners (Table 1). Manganese(III) salts has been considered as the most prominent single-electron oxidant in the field of free-radical chemistry which are commercially available, cheap and easily prepared.[8] When

$Mn(OAc)_3{\cdot}2H_2O$ and $Mn(acac)_3$ were choose as the oxidants in the beginning, the targeted product **3a** was obtained in 37% and 21% yield (entries 1 and 2). The reaction was then performed in a variety of solvents (entries 3–6) by using $Mn(OAc)_3{\cdot}2H_2O$ as the oxidant, such as 1,2-dichloroethane (DCE), *N*-methyl-2-pyrrolidone (NMP), acetonitrile (CH_3CN), and acetic acid (CH_3COOH), giving product **3a** in 30%, 15%, 38% and 55% yield, respectively. Pleasingly, the yield of product **3a** raised to 62% when the temperature was decreased to 60 °C (entry 7). Under this reaction condition, biphenyl was obtained as a by-product, and 10% of **1a** was recovered. However, the yield did not change when the equivalent of **2a** was increased (entry 8). Other oxidants such as $AgNO_3/K_2S_2O_8$, $Mn(OAc)_2$/air, Fe(Ⅱ)/$K_2S_2O_8$, $Mn(OAc)_3$/*t*-BuOOH, $Mn(OAc)_3/KMnO_4$, and $KMnO_4$ were also investigated, but the reaction did not work well under these conditions (entries 9-15). Decreasing the load of $Mn(OAc)_3$ to 2 equiv produced a lower yield of 41% (entry 16). No desired product was obtained when 2.0 equiv of TEMPO was added into the reaction under the optimal conditions (entry 17). This result suggests that the radical was intercepted by TEMPO and this reaction might go through a radical pathway. After optimization of the reaction conditions, we established an efficient route to the carbolactonization of olefinic carboxylic acids. The optimal reaction conditions are: 3.0 equiv of $Mn(OAc)_3{\cdot}2H_2O$ as the oxidant, 1.5 equiv of arylboronic acids and HOAc as the solvent at 60 °C for 6 h under nitrogen atmosphere (entry 7).

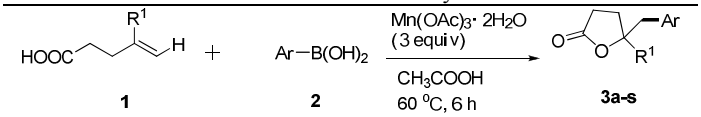
Table 1. Reaction conditions optimization[a]

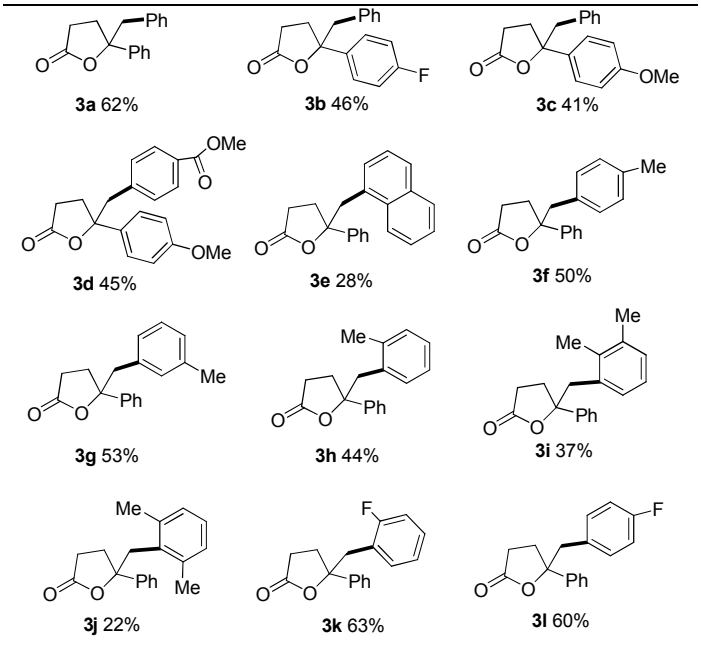


Entry	Additive (equiv)	Solvent	T [°C]	Yield [%]
1	$Mn(OAc)_3{\cdot}2H_2O$ (3)	toluene	100	37
2	$Mn(acac)_3$ (3)	toluene	100	21
3	$Mn(OAc)_3{\cdot}2H_2O$ (3)	DCE	80	30
4	$Mn(OAc)_3{\cdot}2H_2O$ (3)	NMP	80	15
5	$Mn(OAc)_3{\cdot}2H_2O$ (3)	CH_3CN	80	38
6	$Mn(OAc)_3{\cdot}2H_2O$ (3)	HOAc	80	55
7	$Mn(OAc)_3{\cdot}2H_2O$ (3)	HOAc	60	62
8[b]	$Mn(OAc)_3{\cdot}2H_2O$ (3)	HOAc	60	62
9	$AgNO_3$ (0.2) + $K_2S_2O_8$	CH_3CN-H_2O	100	trace
10[c]	$Mn(OAc)_2{\cdot}4H_2O$ (0.05)	DMSO	100	trace
11	FeS(0.5)+$K_2S_2O_8$ (3)	DCM	rt	trace
12	$FeSO_4$(0.2)+$K_2S_2O_8$(3)	PhCl-H_2O (1:1)	rt	n.d
13	$Mn(OAc)_3{\cdot}2H_2O$(1)+*t*-BuOOH(4)	HOAc	60	n.d
14	$Mn(OAc)_3{\cdot}2H_2O$(1)+$KMnO_4$(2)	HOAc	60	26
15	$KMnO_4$(3)	toluene- HOAc (10:1)	100	32
16	$Mn(OAc)_3{\cdot}2H_2O$ (2)	HOAc	60	41
17	$Mn(OAc)_3{\cdot}2H_2O$(3)+TEMPO(2)	HOAc	60	0

[a] *Reaction conditions:* **1a** (0.3 mmol), **2a** (0.45 mmol), additive in solvent (2 mL) stirring under nitrogen for 6 h. Oil bath temperature. Yield of the isolated product. [b]**2a** (0.6 mmol). [c]Under air.

Table 2. Reaction of 4-alkenoic acids with arylboronic acids[a]





[a] *Conditions:* **1** (0.3 mmol), **2** (0.45 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (0.9 mmol), CH_3COOH (2 mL), 6 h, 60 °C (oil bath temperature), under N_2. Isolated yield. [b]**1:** (*E*)-4-phenylbut-3-enoic acid.

Having the optimal conditions in hand, we next examined the reactions of various arylboronic acids with olefinic carboxylic acids to understand the scope of the reaction (Table 2). Readily available 4-arylpent-4-enoic acids with fluoro or methoxy group on the benzene ring were investigated, and the reaction afforded the corresponding γ, γ-disubstituted butyrolactones (**3a–3d**) in moderate to good yields (62–41%). The arylation–lactonization process was compatible with various arylboronic acids. The bulky naphthylboronic acid only gave **3e** in 28% yield. Moreover, the position of methyl group on the benzene ring did not affect this transformation significantly (**3f–3h**). 2,3-Dimethylphenylboronic acid gave **3i** in 37% yield. More bulky substrate like 2,3-dimethylphenylboronic acid also reacted with **1a** and afforded the corresponding product **3j** in much lower yield. Halogen atoms such as fluoro, chloro and bromo at different positions on the aromatic ring (**3k-3o**) were unaffected under the present reaction conditions, providing potential possibility for further functionalization. The substituted phenyl group with electron-donating groups (**3p** and **3q**) and electron-withdrawing groups (**3r** and **3s**) were demonstrated to be applicable and converted into the desired products smoothly. The reaction also worked well with other functional groups such as ester (**3d**), formyl (**3t**) and acetyl (**3u**) resulting in 45%, 57% and 60% yield, respectively. It should be noted that the present carbolactonization is also applicable to unactivated 4-pentenoic acids, giving products **3v** and **3w** in 26% and 32% yield, respectively. Internal alkenoic acid was also investigated, generating the corresponding products **3x** and **3y** in low yields.

In conclusion, we have successfully developed a simple and general method for the preparation of γ, γ-disubstituted butyrolactones through $Mn(OAc)_3$-mediated radical carbolactonization of olefinic carboxylic acids under relatively mild reaction conditions. As one of its notable features, the radical process allows the direct formation of a C-C bond and the construction of a butyrolactone ring in one reaction. Moreover, a variety of useful functional groups are also tolerated, which is attributed to the mild conditions. Finally, the use of a commercially available, cheap and easily prepared $Mn(OAc)_3$ represents an added advantage of this method.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures for the synthesis, spectral data and NMR spectra of compounds **3a-3y**. See DOI: 10.1039/c000000x/

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