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ZnI_2/$Zn(OTf)_2$-TsOH: a versatile combined-acid system for catalytic intramolecular hydrofunctionalization and polyene cyclization†

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A mild and efficient combined-acid system using a zinc(II) salt [ZnI_2 or $Zn(OTf)_2$] and *p*-toluene sulfonic acid (TsOH) was investigated for catalytic cationic cyclizations, including intramolecular hydrocarboxylation, hydroalkoxylation, hydroamination, hydroamidation, hydroarylation and polyene cyclizations. This reaction provides easy access to five- and six-membered O- and N-containing saturated heterocyclic compounds, tetrahydronaphthalene derivatives and polycyclic skeletons in excellent yield with perfect Markovnikov selectivity and under mild conditions. The operational simplicity, broad applicability, and use of inexpensive commercially available catalysts make this protocol superior to existing methodologies.

The fact that ring structures are among the most common components in natural molecules has made cyclization one of the most important classes of reactions in organic synthesis. Synthetic chemists have continually focused in this area on improving existing methodologies and discovering new methods and new reagents, which has led to dramatic advances in the art of ring construction in the last few decades, and this progress shows no signs of tailing off.[1] Among various cyclization strategies, the intramolecular hydrofunctionalization of readily accessible alkenes represents an attractive and atom-economical approach to the formation of carbocyclic and heterocyclic rings. Although a variety of metal and Brønsted acid catalysts have been developed for the additions of N–H,[2] O–H[2h,3] and C(sp^2)–H[4] bonds across olefins, methods based on combinations of acids have rarely been studied but should be considered in this field. First introduced by Yamamoto and Ishihara, the concept of combined acids, which can be classified into Brønsted acid-assisted Lewis acid (BLA), Lewis acid-assisted Lewis acid (LLA), Lewis acid-assisted Brønsted acid (LBA), and Brønsted acid-assisted Brønsted acid (BBA), has been widely used in asymmetric catalysis.[5] The coordination of a Lewis acid or Brønsted acid to the heteroatom of the Brønsted acid could increase the acidity of the latter, and the reactivity and selectivity of the system could also be enhanced by these associative interactions. Accordingly, in our plan, the same principle of the activation of Brønsted acids could play an important role in intramolecular hydrofunctionalizations. Herein, we report a versatile and highly efficient Lewis acid-assisted Brønsted acid (LBA)[5b] system [ZnI_2/$Zn(OTf)_2$ and TsOH] to catalyze the intramolecular hydrocarboxylation, hydroalkoxylation, hydroamination, hydroamidation and hydroarylation of unactivated alkenes and more challenging polyene cyclizations in excellent yields with perfect Markovnikov selectivity (Fig. 1).

During the course of preparing 3-(1-phenylcyclopropyl)-propanoic acid from 4-phenylpent-4-enoic acid (**1a**) with the Simmons-Smith reagent, we serendipitously isolated lactone **2a** as the major product (Scheme 1). After verification, we concluded that the intramolecular hydrocarboxylation should be attributed to the ZnI_2 generated from the Simmons-Smith

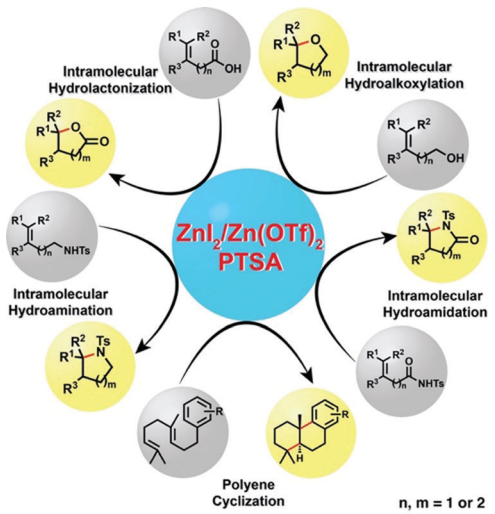

Fig. 1 Combined acid-catalyzed intramolecular hydrofunctionalization of unactivated olefins and polyene cyclizations.

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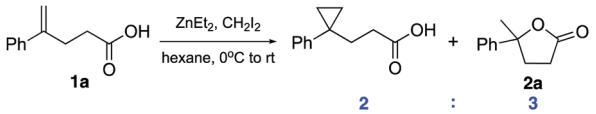
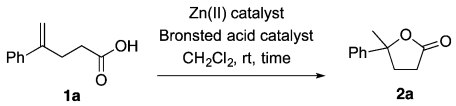


Scheme 1 Isolation of lactone **2a** from Simmons-Smith reaction of **1a**.

Table 1 Optimization of the intramolecular hydrocarboxylation of **1a**



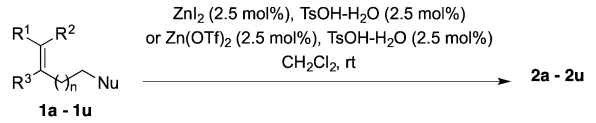
Entry	Zn(II) (mol%)	Brønsted acid (mol%)	Time (h)	Conversion[a] (%)
1	ZnI_2(30)	—	16	40[b]
2	ZnI_2(10)	TsOH·H_2O (10)	1	>99
3	ZnI_2(2.5)	TsOH·H_2O (2.5)	16	>99 (98)
4	ZnI_2(2.5)	TsOH (2.5)	16	>99 (99)
5	$Zn(OTf)_2$(2.5)	TsOH·H_2O (2.5)	1	>99
6	$Zn(OTf)_2$(1.0)	TsOH·H_2O (1.0)	8	>99
7	$Zn(OAc)_2$(10)	TsOH·H_2O (10)	16	0
8	ZnI_2(10)	CF_3COOH (10)	16	12
9	—	TsOH·H_2O (10)	16	66

[a] Yields were determined by ^1H NMR analysis, isolated yield in parentheses.
[b] 40%  was isolated.

reaction system.[6] Indeed, when 30 mol% of ZnI_2 was added to a solution of **1a** in CH_2Cl_2 (Table 1, entry 1), the intramolecular hydrocarboxylation proceeded smoothly at room temperature to afford lactone **2a** (40%) along with the iodolactonization product (40%). With the addition of a catalytic amount of Brønsted acid, either hydrated or anhydrous TsOH, the loading of ZnI_2 could be lowered to 2.5 mol%, and product **2a** was isolated exclusively in quantitative yield (entries 3 and 4). The reagent combination of $Zn(OTf)_2$ and TsOH·H_2O was even more powerful for this transformation, and the catalyst loadings could be further reduced to 1.0 mol% (entry 6). With a less acidic ligand, such as acetate, on the Zn(II) salt, no reaction was observed after 16 h (entry 7). The replacement of TsOH·H_2O with trifluoroacetic acid gave only 12% conversion after 16 h of reaction time (entry 8). Furthermore, the control experiments with 10 mol% TsOH·H_2O showed poor conversion (entry 9), which indicates that combining these acids did bring out their inherent catalytic activity, which was inaccessible with the individual acid catalysts.

The successful use of combined acids in the catalytic intramolecular hydrocarboxylation of **1a** prompted us to examine the suitability of this reaction system for various substrates, and the results are highlighted in Table 2. The combined acids effectively catalyzed 5-*exo*-trig (entries 1–7), 5-*endo*-trig (entries 9 and 10), 6-*exo*-trig (entry 11) and 6-*endo*-trig (entries 12 and 13) hydrocarboxylations at room temperature, and corresponding Markovnikov products **2a**–**2g** and **2i**–**2m** were isolated in excellent yields (92–99%). A higher reaction temperature was required for the cyclization of monosubstituted olefin **1h** (entry 8) in 97% yield. For ring closures involving less acidic hydroxyl (**1n**–**1p**, entries 14–16), amino (**1q**–**1s**, entries 17–19)

Table 2 Substrate scope of the ZnI_2/TsOH- or $Zn(OTf)_2$/TsOH-catalyzed intramolecular hydrofunctionalization of olefins



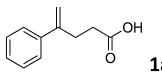
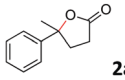
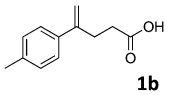
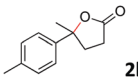
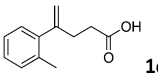
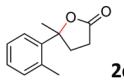
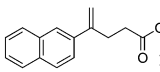
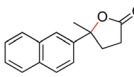
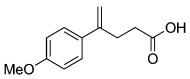
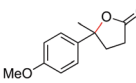
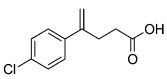
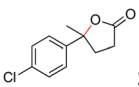
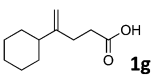
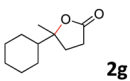
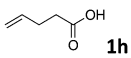
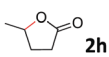
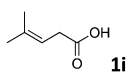
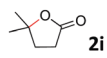
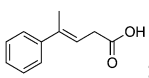
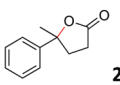
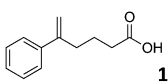
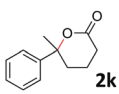
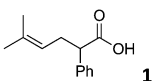
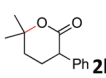
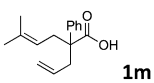
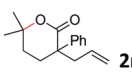
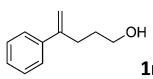
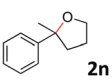
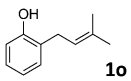
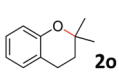
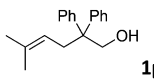
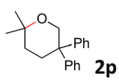
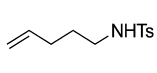
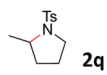
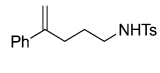
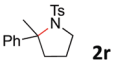
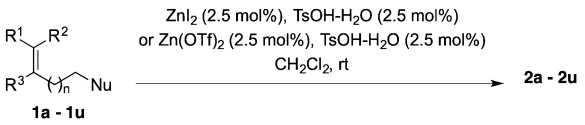
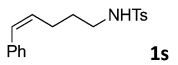
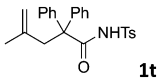
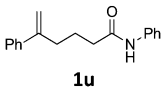
Entry	Substrate	Product	Time (h)	Yield[a] (%)
1[b]	 **1a**	 **2a**	16	98
2[b]	 **1b**	 **2b**	16	99
3[b]	 **1c**	 **2c**	16	94
4[b]	 **1d**	 **2d**	16	98
5[b]	 **1e**	 **2e**	16	94
6[c]	 **1f**	 **2f**	16	99
7[b]	 **1g**	 **2g**	16	98
8[d]	 **1h**	 **2h**	16	97[e]
9[b]	 **1i**	 **2i**	16	94
10[b]	 **1j**	 **2a**	16	93
11[c]	 **1k**	 **2k**	24	92
12[c]	 **1l**	 **2l**	16	94
13[b]	 **1m**	 **2m**	16	94
14[c]	 **1n**	 **2n**	14	94
15[c]	 **1o**	 **2o**	16	94
16[c]	 **1p**	 **2p**	24	93
17[d]	 **1q**	 **2q**	16	92
18[c]	 **1r**	 **2r**	1h	92

Table 2 (*continued*)



Entry	Substrate	Product	Time (h)	Yield[a] (%)
19[d]	 1s	 2s	3	93
20[c]	 1t	 2t	1	99
21[d]	 1u	 2u	24	91

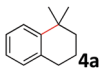
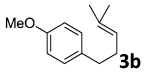
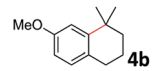
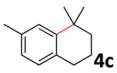
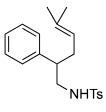
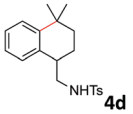
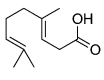
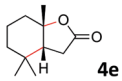
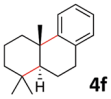
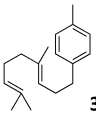
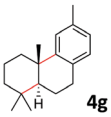
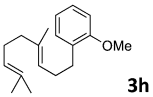
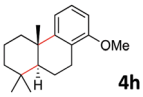
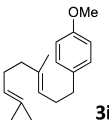
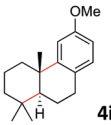
[a] Isolated yield. [b] ZnI_2 (2.5 mol%), $TsOH{\cdot}H_2O$ (2.5 mol%), CH_2Cl_2, rt. [c] $Zn(OTf)_2$ (2.5 mol%), $TsOH{\cdot}H_2O$ (2.5 mol%), CH_2Cl_2, rt. [d] $Zn(OTf)_2$ (2.5 mol%), $TsOH{\cdot}H_2O$ (2.5 mol%), DCE, reflux. [e] GC yield.

and amide (**1t** and **1u**, entries 20 and 21) protons, $Zn(OTf)_2$ (2.5 mol%)–$TsOH{\cdot}H_2O$ (2.5 mol%) was the optimal combined-acid catalyst to give heterocyclic products **2n**–**2u** in 91–99% yields. It is noteworthy that 6-*endo* cyclization was preferred in the case of 1,2-disubstituted *cis*-olefinic **1s** due to the domination of the stable benzylic carbenium intermediate. In general, this simple and mild catalytic system was universally efficient for hydrocarboxylation (entries 1–13), hydroalkoxylation (entries 14–16), hydroamination (entries 17–19), and hydroamidation (entries 20 and 21) reactions with ≥91% isolated yields. Notably, all of these hydrofunctionalizations were highly Markovnikov selective, and no regioisomers were observed. All the reactions except entries 8, 17, 19 and 21, which required a higher reaction temperature (refluxing 1,2-dichloroethane), were carried out in screw-cap vials equipped with a stirring bar at room temperature, and the pure product was quickly obtained after simple filtration through a short pad of silica gel to remove the catalysts.

With the success of the ZnI_2/TsOH- or $Zn(OTf)_2$/TsOH-catalyzed intramolecular hydrofunctionalizations of unactivated olefins, we were interested in extending this catalytic system to hydroarylation and polyene cyclization reactions. To our delight, the reactions of alkenylbenzenes **3a–3d** in the presence of 5 mol% $Zn(OTf)_2$ and 5 mol% $TsOH{\cdot}H_2O$ at room temperature gave tetrahydronaph-thalenes **4a–4d** in 95–99% yields (Table 3, entries 1–4). Interestingly, the isolation of tetrahydronaphthalene **4d** showed that the 6-*endo*-trig hydroarylation was faster than the hydroamination of **3d**. Furthermore, the polycyclization of homogeranic acid (**3e**) was effectively catalyzed by ZnI_2 (10 mol%)–$TsOH{\cdot}H_2O$ (10 mol%) in refluxing dichloromethane, and *cis*-tetrahydroactinidiolide (**4e**) was obtained in 94% yield (entry 5). Finally, homogeranylbenzene (**3f**) and analogues **3g–3i** were tested in the polyene cyclization. Desired *trans*-fused tricyclic compounds **4f–4i** were obtained exclusively in excellent yields (92–99%), and no half-cyclized products were observed.

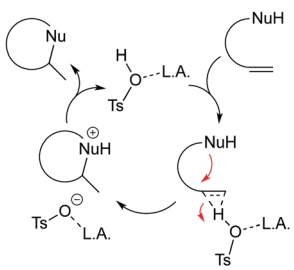
A mechanism of the Lewis acid-assisted Brønsted acid (LBA) catalysis (Scheme 2) is proposed for this system based on a series of observations made during the study. (1) No complexation

Table 3 Substrate scope of the hydroarylation and polyene cyclization reactions

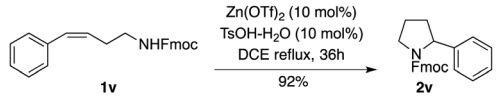
Entry	Substrates	Product	Time (h)	Yield[a] (%)
1[b]	 3a	 4a	1	99
2[b]	 3b	 4b	1	99
3[b]	 3c	 4c	1	95
4[b]	 3d	 4d	16	95
5[c]	 3e (E:Z = 1:0.3)	 4e (all cis)	70	94
6[b]	 3f	 4f	44	92
7[b]	 3g	 4g	14	98
8[b]	 3h	 4h	23	98
9[b]	 3i	 4i	14	99

[a] Isolated yields. [b] $Zn(OTf)_2$ (5 mol%), $TsOH{\cdot}H_2O$ (5 mol%), CH_2Cl_2, rt. [c] ZnI_2 (10 mol%), $TsOH{\cdot}H_2O$ (10 mol%), CH_2Cl_2, reflux.

between Zn cations and the substrates was observed by NMR or mass spectral studies. (2) The electronic effects were the dominant factors controlling the reaction outcomes, especially in the case of diene **1m** and **1s**, which in conjunction with the perfect Markovnikov selectivity observed for all substrates elucidates the nature of the intermediates and suggests a carbenium ion is involved in the mechanism.[7] (3) In the anionic ESI-MS spectra of ZnI_2 and $TsOH{\cdot}H_2O$ dissolved in CH_2Cl_2/THF, $[ZnI_2OTs]^-$ and



Scheme 2 Proposed mechanism for the combined acid catalyzed intramolecular hydrofunctionalization.



Scheme 3 $Zn(OTf)_2$ and $TsOH{\cdot}H_2O$ successfully catalyzed the hydroamination of **1v**.

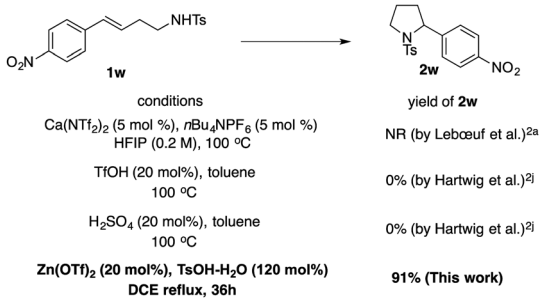


Fig. 2 Direct cross-comparison with reported reaction and the combined-acid reagents.

$[ZnI_3]^-$ signals were observed. Likewise, signals of $[Zn(OTf)_2OTs]^-$ and $[Zn(OTf)_3]^-$ were identified in the mixture of $Zn(OTf)_2$ and $TsOH{\cdot}H_2O$ complexes, which provided direct support for the associative interaction between the Lewis acid and Brønsted acid (see the ESI†). (4) $Zn(OTf)_2$ and $TsOH{\cdot}H_2O$ successfully catalyzed the hydroamination of **1v** to give cyclization product **2v**[2a] in 92% yield (Scheme 3) whereas TfOH, which might be generated *in situ* and acted as a hidden Brønsted acid catalyst,[3g,7,8] was not able to catalyze the same reaction based on Hartwig's report.[2j] Another direct cross-comparison with reported reactions was conducted and is displayed in Fig. 2. The very electron deficient alkene **1w** did not react under the reaction conditions reported by Lebœuf[2a] and Hartwig[2j] respectively. By applying the combined-acid strategy, pyrrolidine **2w** was obtained through intramolecular hydroamination for the first time in 91% yield, which corroborates the advantages of the present catalyst system. The proposed process of LBA catalysis demonstrates that the catalytic activity of the Brønsted acid, TsOH or other protic acids generated *in situ* in these transformations was dramatically increased by the presence of a Lewis acid (Zn(II) salts).

In conclusion, we developed a versatile, highly efficient and environmentally friendly system for the intramolecular hydrofunctionalization of unactivated olefins and polyene cyclizations for the syntheses of saturated heterocycles, tetrahydronaphthalene derivatives and polycyclic compounds in an atom-economical manner. Most of these reactions can be easily conducted in screw-cap vials with stirring bars at room temperature. The low-cost reagents and mild reaction conditions provide high Markovnikov regioselectivity. The mechanism is thought to involve designer acids (Lewis acid-assisted Brønsted acid) that facilitate proton transfer.

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Conflicts of interest

There are no conflicts to declare.

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