Tandem Long Distance Chain-Walking/Cyclization via $RuH_2(CO)(PPh_3)_3$/Brønsted Acid Catalysis: Entry to Aromatic Oxazaheterocycles

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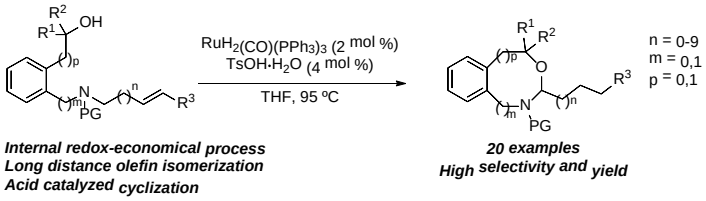


ABSTRACT: A novel route to 1,3-oxazaheterocycles based on cooperative Ru-H/Brønsted acid catalysis is reported. The use of the commercially available $RuH_2(CO)(PPh_3)_3$ complex allows for efficient long distance chain-walking process while the Brønsted acid is responsible for generation of an electrophilic iminium ion which is trapped intramolecularly by an alcohol moiety. The alcohol, besides its nucleophilic function, also plays an important role in the stabilization of the Ru catalyst.

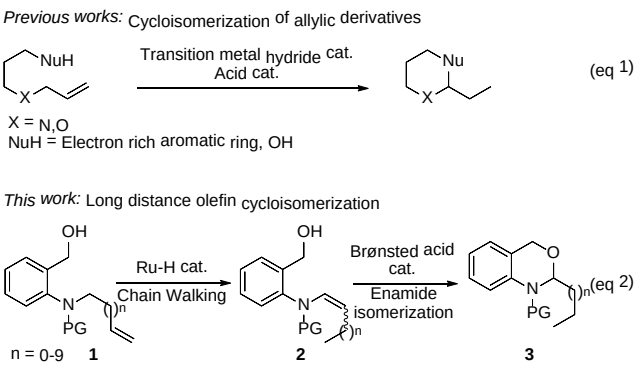
In situ formation of an electrophilic *N*-acyliminium or *N*-sulfonyliminium ion and subsequent trapping with a nucleophile is a well known procedure for the synthesis of a wide range of nitrogen containing heterocycles.[1] Isomerization of enamides under acidic conditions represents a practical strategy for the generation of an *N*-acyliminium ion intermediate. Since the discovery of the self-condensation of enecarbamates by Kobayashi,[2a] enamides have been used as electrophilic precursors in Pictet-Spengler and Mannich-type reactions which lead to α-functionalized amines.[2]

Enamides can be routinely obtained by metal-hydride catalyzed double bond isomerization of easily available allylic amides.[3,4] Complexes of transition metals such as Ru, Rh, Fe, Co or Ir turned out to be active species for the catalytic double bond isomerization of *N*- and *O*-allylic systems.[3,5] Among all catalysts, ruthenium hydride complexes have been particularly useful for the isomerization of *N*-allylamides into the corresponding enamides.[6] In all these cases, the reaction is likely to occur through an olefin coordination, migratory insertion and *β*-hydride elimination sequence.

In 2008 the group of Terada reported a tandem isomerization/C–C bond forming sequence by $RuHCl(CO)(PPh_3)_3$/Brønsted acid cooperative catalysis.[7] The method allows for the isomerization of an *N*-allylamide into a reactive imine which subsequently undergoes a Brønsted acid catalyzed Friedel–Crafts type C–C bond forming reaction under relay catalysis. Following this pioneering work, this methodology was successfully applied in the synthesis of nitrogenated heterocycles by intramolecular trapping of the electrophilic iminium ion intermediate (X = N) with carbon and oxygen nucleophiles (Scheme 1, eq 1).[8,9] More recently, the process has also been extended to generate the less stable oxocarbenium ions (X = O), starting in this case from the corresponding allyl ethers.[10]

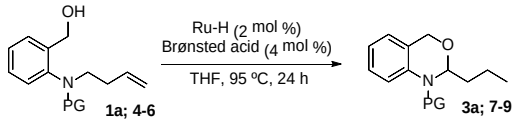
Unfortunately, these synthetic approaches have mostly been limited to allyl derivatives, with the use of longer *N*-substituents leading, in most cases, to a decrease in the reaction yield. Herein we report that the *N*-acyliminium or *N*-sulfonyliminium ions can be efficiently generated by using the commercially available complex $RuH_2(CO)(PPh_3)_3$ as the catalyst for long distance chain-walking olefin isomerization[11] under Ru-H/Brønsted acid cooperative catalysis. We have used this strategy to develop catalytic methodology for the synthesis of benzoxazines **3** (Scheme 1, eq 2); interesting 1,3-oxazaheterocycles which display a wide range of biological activities.[12] The reaction reported proceeds in very good yields and high selectivity and it has also been extended to the synthesis of different oxazaheterocycles.

Scheme 1. Cooperative Ru-H/Brønsted acid catalyzed cycloisomerizations



We began our investigation using *N*-(but-3-en-1-yl)-*N*-(2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide **1a** as model substrate (Table 1).

Table 1. Optimization of catalysts and protecting group



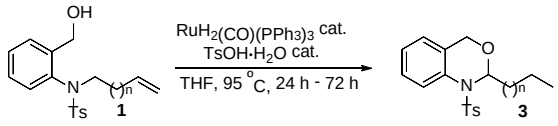
entry[a]	PG	Ru-H	acid	yield (%)[b]
1	Ts, **1a**	$RuHCl(CO)(PPh_3)_3$	$TsOH{\cdot}H_2O$	63, **3a**[c]
2	Ts, **1a**	$[RuH(CO)(PPh_3)_2(MeCN)_2]BF_4$	$TsOH{\cdot}H_2O$	48, **3a**[c]
3	Ts, **1a**	$RuH_2(CO)(PPh_3)_3$	$TsOH{\cdot}H_2O$	88, **3a**
4[d]	Ts, **1a**	$RuH_2(CO)(PPh_3)_3$	$TsOH{\cdot}H_2O$	41, **3a**[c]
5	Ts, **1a**	-	$TsOH{\cdot}H_2O$	-
6	Ts, **1a**	$RuH_2(CO)(PPh_3)_3$	-	93, **2a**
7	Ts, **1a**	$RuH_2(CO)(PPh_3)_3$	$HBF_4{\cdot}OEt_2$	87, **3a**
8[e]	Ts, **1a**	$RuH_2(CO)(PPh_3)_3$	$TsOH{\cdot}H_2O$	86, **3a**
9	Ns, **4**	$RuH_2(CO)(PPh_3)_3$	$TsOH{\cdot}H_2O$	76, **7**
10	Ms, **5**	$RuH_2(CO)(PPh_3)_3$	$TsOH{\cdot}H_2O$	80, **8**
11	Boc, **6**	$RuH_2(CO)(PPh_3)_3$	$TsOH{\cdot}H_2O$	90, **9**

[a] Conditions: **1a** (0.25 mmol), Ru-H (0.005 mmol) and Brønsted acid (0.01 mmol) in 0.5 mL of THF at 95 °C over 24 h. [b] Isolated yields. [c] *N*-crotyl derivative, arising from a single olefin isomerization, was also formed. [d] 70 °C. [e] Starting material recovered. [e]Toluene as solvent.

We first tested Terada's catalyst system, $RuHCl(CO(PPh_3)_3$, which has shown good iminium ion generation from *N*-allylic systems.[7,8a] Cycloisomerization of **1a** to the corresponding 1,3-benzoxazine **3a** took place in the presence of $TsOH{\cdot}H_2O$ (4 mol%), although in moderate yield arose from incomplete olefin isomerization (entry 1). A lower yield was obtained with the cationic ruthenium monohydride catalyst $[RuH(CO(PPh_3)_2(MeCN)_2]BF_4$ (entry 2). To our delight, the ruthenium dihydride catalyst, $RuH_2(CO)(PPh_3)_3$ (2 mol %),[13] proved to be more active under the same reaction conditions with cycloisomerization occurring smoothly to give benzoxazine **3a** in very good yield (entry 3). The reaction temperature played a significant role in the cycloisomerization process, with a slight decrease of the temperature leading to a significant drop in the reaction yield (entry 4). Both the ruthenium hydride and Brønsted acid catalysts were crucial to trigger the cycloisomerization process. Without the ruthenium catalyst, the starting material **1a** was recovered (entry 5). As expected, in the absence of acid, the olefin isomerization smoothly occurred to give the conjugated tosyl enamide **2a**, but without subsequent cyclization (entry 6). Other strong Brønsted acids (HBF_4, TfOH) and Lewis acids ($BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, $In(OTf)_3$) also proved to be efficient catalysts for this transformation (entry 7 and Table S2). Finally, a survey of solvents showed that toluene could alternatively be used without yield erosion (entry 8) while the use of chlorinated solvents or DMF led to a significant decrease in catalyst activity (see Supporting Information). Our cycloisomerization reaction could also be satisfactorily performed with other sulfonamide protecting groups (entries 9-11), like nosyl and methylsulfonyl amides **4** and **5** (PG = Ns, Ms) in 76% and 80% yields, respectively. In addition, **6** (PG = Boc) was also extremely well tolerated to give benzoxazine **9** in 90% yield, without formation of any traces of deprotected amine (entry 11).[14]

Long distance chain-walking olefin isomerization was analyzed next (Table 2). As expected, the isomerization of *N*-allyl derivative **1b** (n = 0) was perfectly accomplished to afford the benzoxazine **3b** in an excellent 93% yield (entry 1). Gratifyingly, *bis*-, *tris*- and *tetra*-homoallyl derivatives **1c-e** (*n* = 2, 3 and 4) smoothly cycloisomerized to benzoxazines **3c-e** in fairly good yields (entries 3-5), although longer reaction times were needed.[15] To our delight, the cycloisomerization also took place even in a remotely functionalized olefin **1f** (*n* = 9), although extra loading of catalysts (Ru 8 mol%, TsOH 10 mol%) and longer reaction time (72 h) were needed (entry 6).

Table 2. Chain-walking olefin isomerization

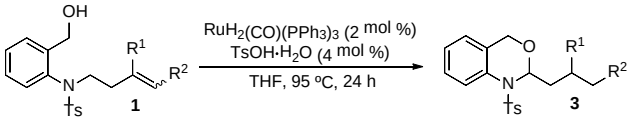


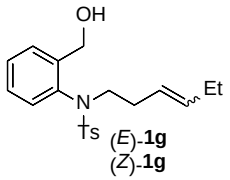
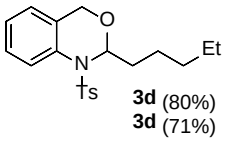
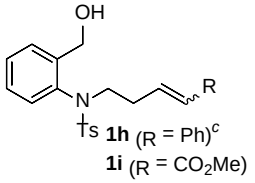
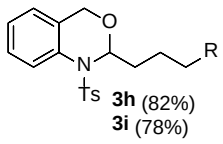
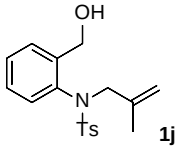
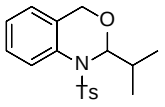
entry[a]	n	$RuH_2(CO)(PPh_3)_3$	$TsOH{\cdot}H_2O$	time (h)	yield (%)[b]
1	0, **1b**	2 mol %	4 mol %	24	93, **3b**
2	1, **1a**	2 mol %	4 mol %	24	88, **3a**
3	2, **1c**	2 mol %	4 mol %	48	82, **3c**
4	3, **1d**	2 mol %	4 mol %	48	76, **3d**
5	4, **1e**	4 mol %	6 mol %	48	80, **3e**
6	9, **1f**	8 mol %	10 mol %	72	41, **3f**

[a] Conditions: **1a-f** (0.25 mmol), $RuH_2(CO)(PPh_3)_3$ and $TsOH{\cdot}H_2O$ in 0.5 mL of THF at 95 °C. [b] Isolated yields.

We next set out to investigate the scope of the reaction with respect to the alkene-bearing chain (Table 3).

Table 3. Variations in alkene-bearing chain



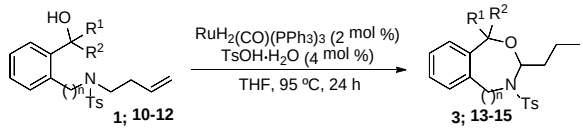
entry[a]	substrate	Product [b]
1	 (*E*)-**1g** (*Z*)-**1g**	 **3d** (80%) **3d** (71%)
2	 **1h** (R = Ph)[c] **1i** ($R = CO_2Me$)	 **3h** (82%) **3i** (78%)
3[d]	 **1j**	 **3j** (50%)

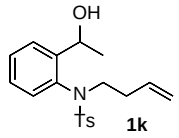
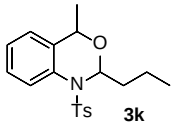
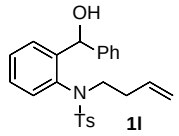
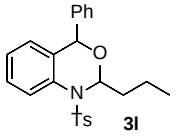
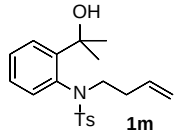
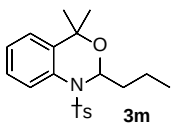
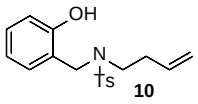
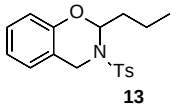
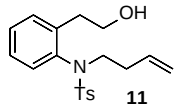
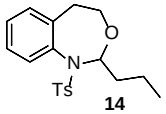
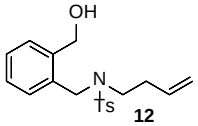
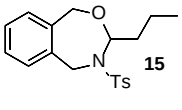
[a] Conditions: **1g-j** (0.25 mmol), $RuH_2(CO)(PPh_3)_3$ (0.005 mmol) and $TsOH{\cdot}H_2O$ (0.01 mmol) in 0.5 mL of THF, 24 h at 95 °C. [b] Isolated yields. [c] $RuH_2(CO)(PPh_3)_3$ 5 mol %, $TsOH{\cdot}H_2O$ 7 mol %, in 0.3 mL of toluene, 24 h at 110 °C. [d] **1j** (0.15 mmol), $RuH_2(CO)(PPh_3)_3$ 10 mol %, $TsOH{\cdot}H_2O$ 12 mol %, in 0.3 mL of toluene, 72 h at 110 °C.

We found that both (*E*)- and (*Z*)-1,2-disubstituted alkenes were competent substrates for this transformation as illustrated by the synthesis of benzoxazine **3d** (Table 3, entry 1). Pleasingly, the more challenging styryl and conjugated ester derivatives **1h** and **1i** were also able to cycloisomerize to the corresponding benzoxazines **3h** and **3i** in good yield (entry 2), thus showing the high activity of this catalytic system. A 1,1-disubstituted alkene, such as **1j**, was likewise compatible with this transformation, although it showed a diminished reactivity, providing **3j** in moderate yield (entry 3).[16]

Finally, different types of oxygenated nucleophiles were analyzed (Table 4). Thus, secondary **1k** and **1l** and even tertiary alcohols **1m** cycloisomerized to their corresponding benzoxazines **3k**, **3l** and **3m** in fairly good yields, albeit with modest diastereoselectivities (entries 1-3). Phenol **10** was also an efficient substrate and provided benzoxazine **13** in excellent yield (entry 4). Gratifyingly, seven-membered benzoxazepines **14** and **15** could also be synthesized by this procedure by both elongating the hydroxyl chain (**11**, entry 5) or by using a benzyl amide derivative (**12**, entry 6).

Table 4. Scope of the oxygenated nucleophile

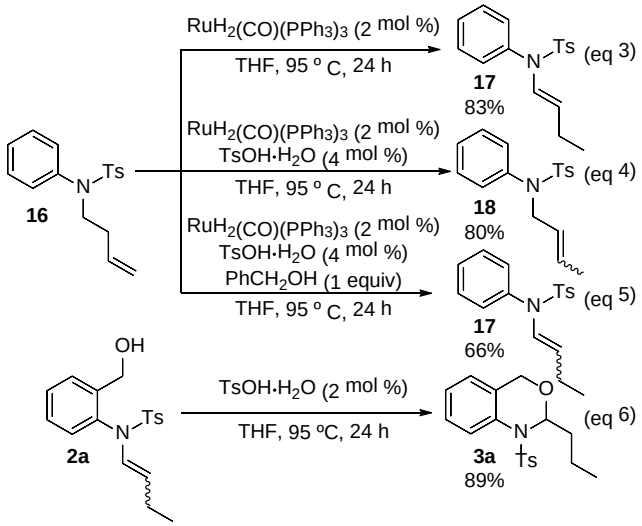


entry[a]	substrate	product	yield (%)[b]
1	 **1k**	 **3k**	70 (dr 1.7:1)
2[c]	 **1l**	 **3l**	71 (dr 1.8:1)
3[c]	 **1m**	 **3m**	62
4	 **10**	 **13**	91
5	 **11**	 **14**	79
6[d]	 **12**	 **15**	71

[a] Conditions: Substrate (0.25 mmol), $RuH_2(CO)(PPh_3)_3$ (2 mol %, 0.005 mmol) and $TsOH{\cdot}H_2O$ (4 mol %, 0.01 mmol) in 0.5 mL of THF, 24 h, 95 ºC. [b] Isolated Yields. [c] **1l** or **1m** (0.25 mmol), $RuH_2(CO)(PPh_3)_3$ 5 mol %, $TsOH{\cdot}H_2O$ 7 mol %, 110 ºC. [d] **12** (0.15 mmol), $RuH_2(CO)(PPh_3)_3$ 5 mol %, $TsOH{\cdot}H_2O$ 7 mol %, 95 ºC.

Reactions performed with *N*-(but-3-en-1-yl)-*N*-phenyl-4-methylbenzenesulfonamide **16,** the parent dehydroxy derivative, provided valuable insight into the mechanism of the reaction (Scheme 2). The chain-walking process is triggered by the catalyst $RuH_2CO(PPh_3)_3$ without the need of external acid, since **16** gave the isomeric enamide **17** (mixture of *E*/*Z* isomers) in 83% yield after heating in THF at 95 ºC for 24 h (eq 3). In contrast, the reaction of **16** with the same catalyst, but in the presence of catalytic amounts of TsOH, gave the isomeric *N*-(but-2-en-1-yl)tosylamide **18** in 80% yield (mixture of *E*/*Z* isomers), in which only one "step-walk" took place (eq 4). Therefore, the presence of a protic acid is deleterious for the chain-walking event possibly by forming inactive catalytic ruthenium species. Interestingly, adding one equivalent of benzylic alcohol to the last mixture allowed the recovery of the catalytic activity of the ruthenium hydride species giving again efficiently the isomeric enamide **17** (eq 5). Therefore, it seems that the alcohol functionality (in this case, intermolecularly) acts as a crucial ligand for the ruthenium catalysts while also preventing the formation of inactive species in the presence of acid.[17] On the other hand, tosyl enamide **2a** could be efficiently cycloisomerized to benzoxazine **3a** in the presence of catalytic amounts of $TsOH{\cdot}H_2O$ (eq 6), which means that both reaction steps, chain-walking and cycloisomerization, are independently catalyzed by ruthenium hydride complexes and by acid, respectively.

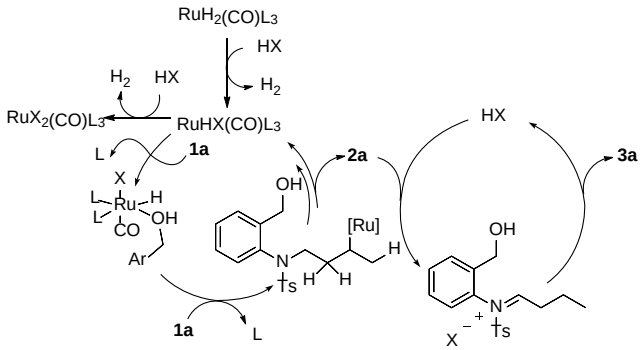
Scheme 2. Mechanistic investigations



In order to account for the observed data, the following catalytic cycle is proposed (Scheme 3). Following the formation of the active Ru(II) hydride complex, $Ru(H)X(CO)L_3$,[13] coordination through the alcohol unit of alkenylamide **1a**, facilitates the chain-walking event (inter- or intramolecularly) to give enamide **2a** with recovery of the catalytic Ru(II)-H species. Subsequently, enamide **2a** enters into an independent acid-catalyzed cycle to give the cycloisomerized benzoxazine **3a** with recovery of the proton carrier.[18] On the other hand, in absence of the alcohol ligand and under acidic conditions, $Ru(H)X(CO)L_3$ catalyst might be slowly deactivated to give, most likely, the Ru(II) complex $RuX_2(CO)L_3$ which stops the chain-walking process. In the absence of acid, the starting Ru(II) complex $RuH_2(CO)L_3$ is able to isomerize the starting alkenylamide **1a** to the enamide **2a** through a typical chain-walking isomerization process (iterative insertions of an alkene into a Ru-H bond followed by β-elimination to give a new Ru-H and an

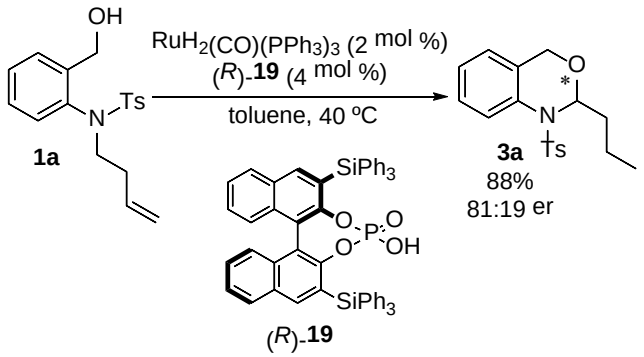
alkene until the formation of the more thermodynamically stable olefin).

Scheme 3. Proposed catalytic cycle



Preliminary studies on an enantioselective variant with chiral Brønsted acid of this tandem isomerization/cyclization showed promising results (Scheme 4).[19,20] It was found that the use of chiral phosphoric acid (*R*)-**19** in combination with $RuH_2(CO)PPh_3$ (see Supporting Information for further details) gave rise to benzoxazine **3a** with encouraging levels of enantioselectivity (81:19 er). Interestingly, this phosphoric acid also allowed the reaction to be performed under reduced temperature (40 ºC) with full conversion and selectivity.[21] This positive result paves the way for an asymmetric method to synthesize 1,3-oxazaheterocycles and represents the first example of an enantioselective tandem Ru-H/chiral Brønsted acid catalyzed process in which an *N*-homoallyl amide is used.

Scheme 4. Enantioselective cycloisomerization



In summary, we have reported a novel catalytic procedure for the synthesis of six- and seven-membered 1,3-oxazaheterocycles through a simple, redox-economical dual Ru-H /Brønsted acid catalyzed cycloisomerization of 2-hydroxy(alkyl) substituted *N*-alkenyl aniline and benzylamine derivatives. The use of the commercially available $RuH_2(CO)(PPh_3)_3$ complex enables an efficient long-distance chain-walking process, thus allowing a wide range of 2-alkylsubstituted 1,3-oxazaheterocycles to be obtained in very good yields. We have found that the hydroxyl unit, besides its nucleophilic function, plays also an important role in the stabilization of the Ru catalyst. In addition, preliminary studies show that 1,3-oxazaheterocyles can be obtained in an enantioselective fashion by using a chiral phosphoric acid, which provides space for further study of this asymmetric variant.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral data of all products.

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Author Contributions

The authors declare no competing financial interest.

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(14) Carboxybenzyl (Cbz) and acetyl (Ac) protected amides **12** and **13** failed to give the corresponding cyclization products.
(15) Starting with **1c**, isomerization of *N*-4-penten-1-yl to *N*-[(*E*)-3-penten-1-yl] isomer was observed when using non-hydride ruthenium catalysts (only one "step-walk"). See ref 4.
(16) No cycloisomerization occurred when a substrate containing a *N*-(3-methyl-3-butenyl) chain was used.
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(20) For examples on enantioselective tandem ruthenium-hydride/chiral Brønsted acid catalyzed cycloisomerizations of *N*-allyl derivatives, see references 8a, 8b, 9b and 9c.
(21) Heating the enantiomeric mixture of **3a** under the reaction conditions for 24 h gave no epimerization. See Supporting Information for details.