Organic LETTERS

Letter

pubs.acs.org/OrgLett

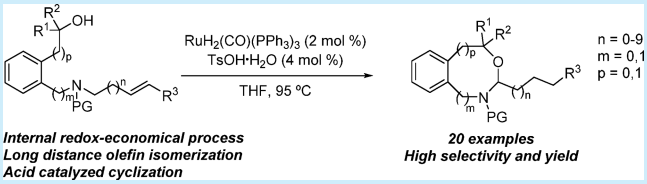
# Tandem Long Distance Chain-Walking/Cyclization via $RuH_2(CO)(PPh_3)_3$/Brønsted Acid Catalysis: Entry to Aromatic Oxazaheterocycles

Rodrigo Bernárdez, Jaime Suárez, Martín Fañanás-Mastral, Jesús A. Varela, and Carlos Saá*

Departamento de Química Orgánica y Centro Singular de Investigación en Química Biológica y Materiales Moleculares (CIQUS), Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

Supporting Information

**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 an 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.





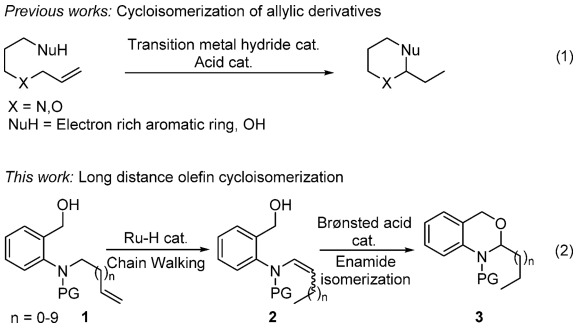

*In situ* formation of an electrophilic *N*-acyliminium or *N*-sulfonyliminium ion and subsequent trapping with a nucleophile is a well-known procedure for the synthesis of a wide range of nitrogen-containing heterocycles.[1] Isomerization of enamides under acidic conditions represents a practical strategy 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 $\alpha$-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 $\beta$-hydride elimination sequence.

In 2008 the Terada group 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 C and O 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*-acyl- 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 displaying a wide range of biological activities.[12] The reaction reported proceeds in very good yields and high selectivity and 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 the model substrate (Table 1).

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-

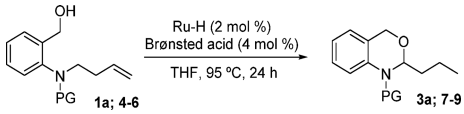
**Received:** December 9, 2015
**Published:** February 1, 2016





DOI: 10.1021/acs.orglett.5b03499
*Org. Lett.* 2016, 18, 642−645

**Table 1. Optimization of Catalysts and Protecting Group**



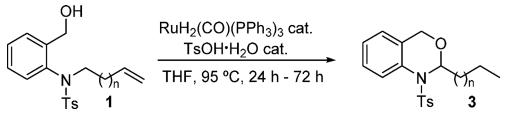

| entry[a] | PG | Ru−H | acid | yield (%)[b] |
|---|---|---|---|---|
| 1 | Ts, **1a** | $RuHCl(CO)(PPh_3)_3$ | $TsOH·H_2O$ | 63, **3a**[c] |
| 2 | Ts, **1a** | $[RuH(CO)(PPh_3)_2(MeCN)_2]BF_4$ | $TsOH·H_2O$ | 48, **3a**[c] |
| 3 | Ts, **1a** | $RuH_2(CO)(PPh_3)_3$ | $TsOH·H_2O$ | 88, **3a** |
| 4[d]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

benzoxazine **3a** took place in the presence of $TsOH·H_2O$ (4 mol %), although in moderate yield which 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 Ru 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 ($BF_3·OEt_2$, $Sc(OTf)_3$, $In(OTf)_3$) also proved to be efficient catalysts for this transformation (entry 7; 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 (Supporting Information (SI)). Our cycloisomerization reaction could also be satisfactorily performed with other sulfonamide protecting groups (entries 9−11), such as nosyl and methylsulfonyl amides **4** and **5** (PG = Ns, Ms) in 76% and 80% yields, respectively. **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

**Table 2. Chain-Walking Olefin Isomerization**



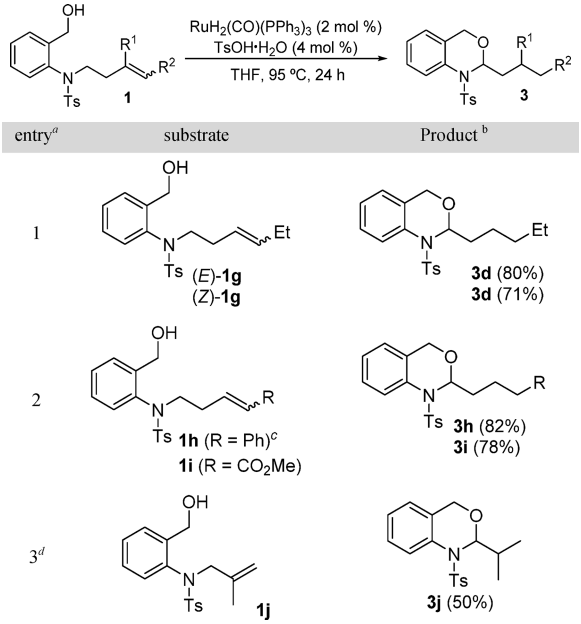

| entry[a] | $n$ | $RuH_2(CO)(PPh_3)_3$ | $TsOH·H_2O$ | time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 0, **1b** | 2 mol % | 4 mol % | 24 | 93, **3b** |
| 2 | 1, **1a** | 2 mol % | 4 mol % | 24 | 88, **3a** |
| 3 | 2, **1c** | 2 mol % | 4 mol % | 48 | 82, **3c** |
| 4 | 3, **1d** | 2 mol % | 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 $TsOH·H_2O$ in 0.5 mL of THF at 95 °C. [b]Isolated yields.

loading of catalysts (Ru 8 mol %, TsOH 10 mol %) and a longer reaction time (72 h) were needed (entry 6).

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**




[a]Conditions: **1g**−**j** (0.25 mmol), $RuH_2(CO)(PPh_3)_3$ (0.005 mmol), and $TsOH·H_2O$ (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 %, $TsOH·H_2O$ 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 %, $TsOH·H_2O$ 12 mol %, in 0.3 mL of toluene, 72 h at 110 °C.

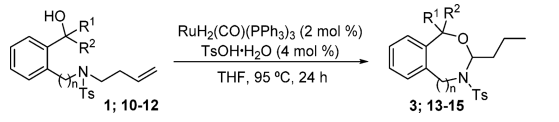
We found that both (*E*)- and (*Z*)-1,2-disubstituted alkenes were competent substrates for this transformation as illustrated by the synthesis of benzoxazine **3d** (Table 3, entry 1). Pleasingly, the more challenging styryl and conjugated ester derivatives **1h** and **1i** were also able to cycloisomerize 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]

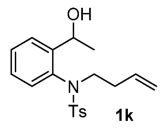
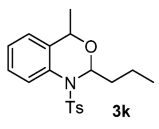
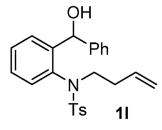
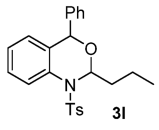
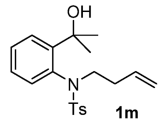
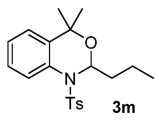
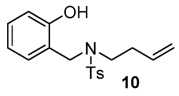
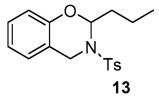
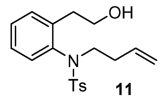
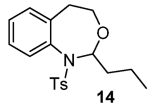
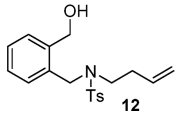
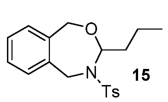
Finally, different types of oxygenated nucleophiles were analyzed (Table 4). Thus, secondary (**1k** and **1l**) and even



DOI: 10.1021/acs.orglett.5b03499
*Org. Lett.* 2016, 18, 642−645

**Table 4. Scope of the Oxygenated Nucleophile**



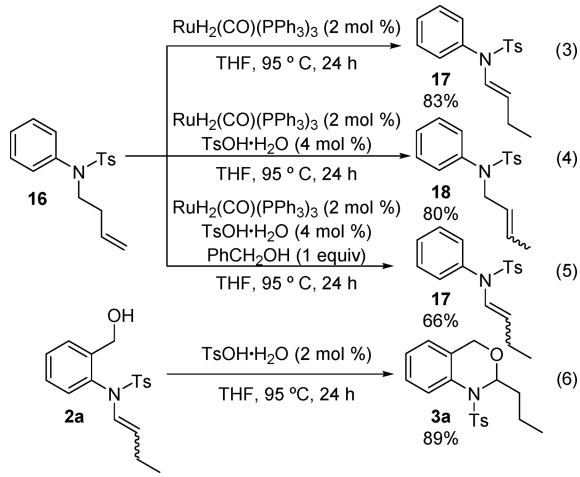

| entry[a] | substrate | product | yield (%)[b] |
|---|---|---|---|
| 1 |  1k |  3k | 70 (dr 1.7:1) |
| 2[c] |  1l |  3l | 71 (dr 1.8:1) |
| 3[c] |  1m |  3m | 62 |
| 4 |  10 |  13 | 91 |
| 5 |  11 |  14 | 79 |
| 6[d] |  12 |  15 | 71 |

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

tertiary (**1m**) alcohols cycloisomerized to their corresponding benzoxazines **3k−m** 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 elongating the hydroxyl chain (**11**, entry 5) or using a benzyl amide derivative (**12**, entry 6).

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 for external acid, since **16** gave the isomeric enamide **17** (mixture of *E*/*Z* isomers) in 83% yield after heating in THF at 95 °C 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 1 equiv of benzylic alcohol to the last mixture allowed the recovery of the catalytic activity of the ruthenium hydride species giving again efficiently

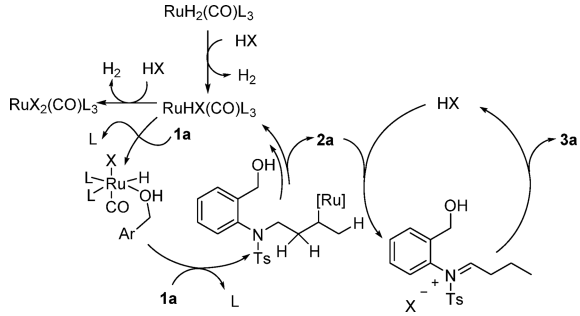
**Scheme 2. Mechanistic Investigations**




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 $TsOH·H_2O$ (eq 6), which means that both reaction steps, chain-walking and cycloisomerization, are independently catalyzed by ruthenium hydride complexes and by acid, respectively.

To account for the observed data, the following catalytic cycle is proposed (Scheme 3). Following the formation of the active

**Scheme 3. Proposed Catalytic Cycle**



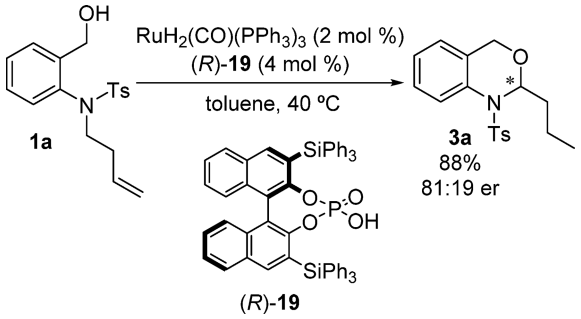

Ru(II) hydride complex, $Ru(H)X(CO)L_3$,[13] coordination through the alcohol unit of alkenylamide **1a** facilitates the chain-walking event (inter- or intramolecularly) to give enamide **2a** with recovery of the catalytic Ru(II)−H species. Subsequently, **2a** enters into an independent acid-catalyzed cycle to give the cycloisomerized benzoxazine **3a** with recovery of the proton carrier.[18] On the other hand, in the absence of the alcohol ligand and under acidic conditions, the $Ru(H)X(CO)L_3$ 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 **2a** through a typical chain-walking isomerization process (iterative insertions of an alkene into a Ru−H bond followed by $\beta$-elimination to give a new Ru−H and an alkene until the formation of the more thermodynamically stable olefin).

Preliminary studies on an enantioselective variant with a chiral Brønsted acid of this tandem isomerization/cyclization showed promising results (Scheme 4).[19,20] It was found that the use of



DOI: 10.1021/acs.orglett.5b03499
*Org. Lett.* 2016, 18, 642−645

**Scheme 4. Enantioselective Cycloisomerization**




chiral phosphoric acid (*R*)-**19** in combination with $RuH_2(CO)(PPh_3)_3$ (SI) 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 °C) 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.

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-oxazaheterocycles 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 at DOI: 10.1021/acs.orglett.5b03499.

Experimental procedures, spectral data of all products (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: carlos.saa@usc.es.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by MINECO (Spain) (Projects CTQ2011-28258 and CTQ2014-59015R), Xunta de Galicia (Project GRC2014/032), and the European Regional Development Fund (Projects CTQ2014-59015R and GRC2014/032). R.B. thanks MEC for a predoctoral FPU fellowship, and J.S. thanks XUGA for a postdoctoral contract. M.F.-M. thanks MINECO for a "Ramón y Cajal" contract.

## ■ REFERENCES

(1) (a) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311. (c) Kataja, A.; Masson, G. O. *Tetrahedron* **2014**, *70*, 8783.

(2) (a) Kobayashi, S.; Gustafsson, T.; Shimizu, Y.; Kiyohara, H.; Matsubara, R. *Org. Lett.* **2006**, *8*, 4923. (b) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292. (c) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565. (d) Terada, M.; Tanaka, H.; Sorimachi, K. *Synlett* **2008**, *2008*, 1661.

(3) (a) Escoubet, S.; Gastaldi, S.; Bertrand, M. *Eur. J. Org. Chem.* **2005**, *2005*, 3855. (b) Krompiec, S.; Krompiec, M.; Penczek, H.; Ignasiak, H. *Coord. Chem. Rev.* **2008**, *252*, 1819.

(4) For a non-Ru−H catalyzed isomerization, see: Larsen, C. R.; Grotjahn, D. B. *J. Am. Chem. Soc.* **2012**, *134*, 10357.

(5) Kuznik, N.; Krompiec, S. *Coord. Chem. Rev.* **2007**, *251*, 222.

(6) (a) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139. (b) Krompiec, S.; Pigulla, M.; Kuznik, N.; Krompiec, M.; Marciniec, B.; Chadyniak, D.; Kasperczyk, J. *J. Mol. Catal. A: Chem.* **2005**, *225*, 91. (c) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255.

(7) Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2008**, *130*, 14452.

(8) (a) Toda, Y.; Terada, M. *Synlett* **2013**, *24*, 752. (b) Hansen, C. L.; Clausen, J. W.; Ohm, R. G.; Ascic, E.; Le Quement, S. T.; Tanner, D.; Nielsen, T. E. *J. Org. Chem.* **2013**, *78*, 12545. (c) For a review, see: Ishoey, M.; Nielsen, T. E. *Chem. - Eur. J.* **2014**, *20*, 8832.

(9) For tandem cycloisomerizations catalyzed by Hoveyda−Grubbs complexes, see: (a) Ascic, E.; Jensen, J. F.; Nielsen, T. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 5188. (b) Cai, Q.; Liang, X.-W.; Wang, S.-G.; You, S.-L. *Org. Lett.* **2012**, *14*, 5022. (c) Cai, Q.; Liang, X.-W.; Wang, S.-G.; You, S.-L. *Org. Biomol. Chem.* **2013**, *11*, 1602. For $RhCl(PPh_3)_3$ catalyzed cycloisomerizations: (d) Ascic, E.; Hansen, C. L.; Le Quement, S. T.; Nielsen, T. E. *Chem. Commun.* **2012**, *48*, 3345.

(10) (a) Lombardo, V. M.; Thomas, C. D.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 12910. (b) Ascic, E.; Ohm, R. G.; Petersen, R.; Hansen, M. R.; Hansen, C. L.; Madsen, D.; Tanner, D.; Nielsen, T. E. *Chem. - Eur. J.* **2014**, *20*, 3297.

(11) For Pd−H catalyzed long distance chain walking of alkenes and alkenyl alcohols, see: (a) Kochi, T.; Hamasaki, T.; Aoyama, Y.; Kawasaki, J.; Kakiuchi, F. *J. Am. Chem. Soc.* **2012**, *134*, 16544. (b) Larionov, E.; Lin, L.; Guénée, L.; Mazet, C. *J. Am. Chem. Soc.* **2014**, *136*, 16882. (c) Mei, T.-S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340.

(12) (a) Schwenker, G.; Chen, J. *Arch. Pharm.* **1991**, *324*, 891. (b) Zhang, P.; Terefenko, E. A.; Fensome, A.; Zhang, Z.; Zhu, Y.; Cohen, J.; Winneker, R.; Wrobel, J.; Yardley, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 787. (c) Ouberai, M.; Asche, C.; Carrez, D.; Croisy, A.; Dumy, P.; Demeunynck, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4641.

(13) Zbieg, J. R.; Yamaguchi, E.; McInturff, E.; Krische, M. J. *Science* **2012**, *336*, 324.

(14) Carboxybenzyl (Cbz) and acetyl (Ac) protected amides and failed to give the corresponding cyclization products.

(15) Starting with **1c**, isomerization of the *N*-4-penten-1-yl to *N*-[(*E*)-3-penten-1-yl] isomer was observed when using nonhydride 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.

(17) For a related stabilization, see: Perdriau, S.; Chang, M.-C.; Otten, E.; Heeres, H. J.; de Vries, J. G. *Chem. - Eur. J.* **2014**, *20*, 15434.

(18) For other catalytic combinations using lower amounts of a Brønsted acid, incomplete cycloisomerizations were found (see SI).

(19) For a review on the use of chiral Brønsted acids in asymmetric transformations, see: Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.

(20) For examples on enantioselective tandem ruthenium-hydride/chiral Brønsted acid catalyzed cycloisomerizations of *N*-allyl derivatives, see refs 8a, 8b, 9b, and 9c.

(21) Heating the enantiomeric mixture of **3a** under the reaction conditions for 24 h gave no epimerization (see SI).



DOI: 10.1021/acs.orglett.5b03499
*Org. Lett.* 2016, 18, 642−645