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Sequential Ruthenium Catalysis for Olefin Isomerization and Oxidation: Application to the Synthesis of Unusual Amino Acids

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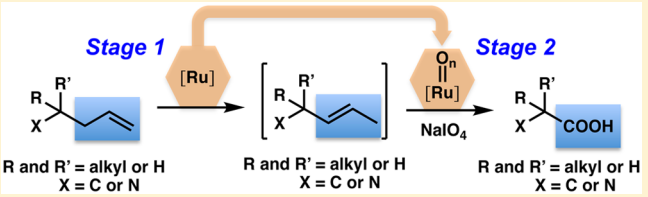
Supporting Information

ABSTRACT: How can you use a ruthenium isomerization catalyst twice? A ruthenium-catalyzed sequence for the formal two-carbon scission of allyl groups to carboxylic acids has been developed. The reaction includes an initial isomerization step using commercially available ruthenium catalysts followed by *in situ* transformation of the complex to a metal-oxo species, which is capable of catalyzing subsequent oxidation reactions. The method enables enantioselective syntheses of challenging α-tri- and tetrasubstituted α-amino acids including an expedient total synthesis of the antiepileptic drug levetiracetam.



INTRODUCTION

The use of a single metal catalyst for several chemical transformations in a one-pot and/or a sequential manner[1] is highly desirable due to high material cost and limited resources of transition metals.[2] Moreover, new tools for modifying prevalent functional groups, which are easily installed in a chemo- and stereoselective fashion, are needed to expand the application of novel methodology in both academic and industrial settings.[3] In this context, allyl groups are ubiquitous and their introduction is very well established including asymmetric additions.[4] In general, three modes for their installation can be distinguished (Figure 1): as a nucleophile[5,6] (e.g., Grignard addition[7]), as an electrophile[8] (e.g., Tsuji–Trost allylation[9]), or as a formally neutral species[10] (e.g., Keck radical allylation[11]).

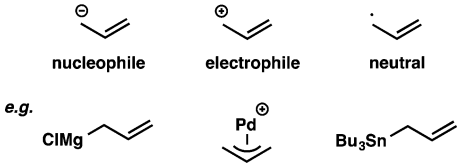
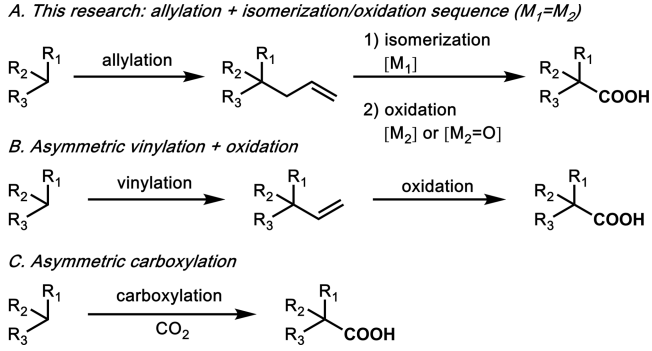


Figure 1. General modes for the introduction of allyl groups.

Most of these methods not only find widespread use in organic synthesis but also allow for the installation of allyl groups in a highly stereoselective fashion, even to build challenging chiral quaternary stereocenters.[12] However, tools for the formal scission of two carbons of an allyl group leading to a truncated carboxylic acid using a single transition metal catalyst have, to our knowledge, not been described (Scheme 1A, $M_1 = M_2$). The use of only one catalyst is in strong contrast to the field of one-pot catalysis, where for instance two transition metal catalysts are used for isomerization/metathesis reactions.[13]

Scheme 1. Sequences and Methods for the Introduction of Chiral Carboxylic Acid Groups



Although a sequence involving vinylation followed by oxidative cleavage of the double bond would in theory lead to the same carboxylic acid product, asymmetric vinylation reactions are far less established than allylations (Scheme 1B).[4] In particular, catalytic enantioselective vinylation of carbonyl enolates is still highly challenging and limited in substrate scope, and, moreover, methods for the construction of quaternary stereocenters are very rare.[12,14] Even more scarce and far less established are catalytic enantioselective carboxylations (Scheme 1C).[15]

As a result, we focused our attention on the catalytic oxidative scission of two carbons from the tail of an allyl unit in order to render such groups as carboxylic acid synthetic equivalents (Scheme 2). Herein, we present the results of that study and provide illustrative examples of this new method in the context of high value and unusual amino acid synthesis.

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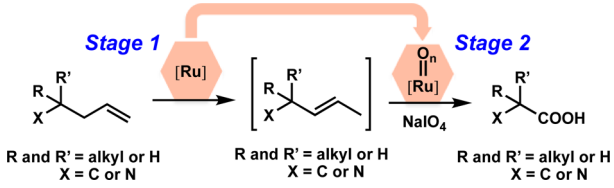
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 2. Ruthenium-Catalyzed Two-Carbon Truncation of Allyl Groups to Carboxylic Acids



RESULTS AND DISCUSSION

After exploring a variety of transition metal catalysts known for alkene isomerization (iridium, rhodium, palladium, ruthenium; for details see the Supporting Information), we found that ruthenium catalysts performed best and were amenable to further oxidative catalysis (Scheme 2).

In particular, the commercially available Grubbs second-generation catalyst **1a** (Figure 2) under Nishida's conditions[16]

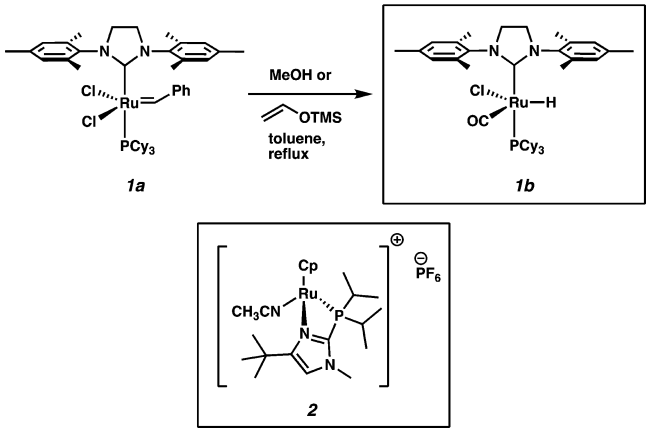


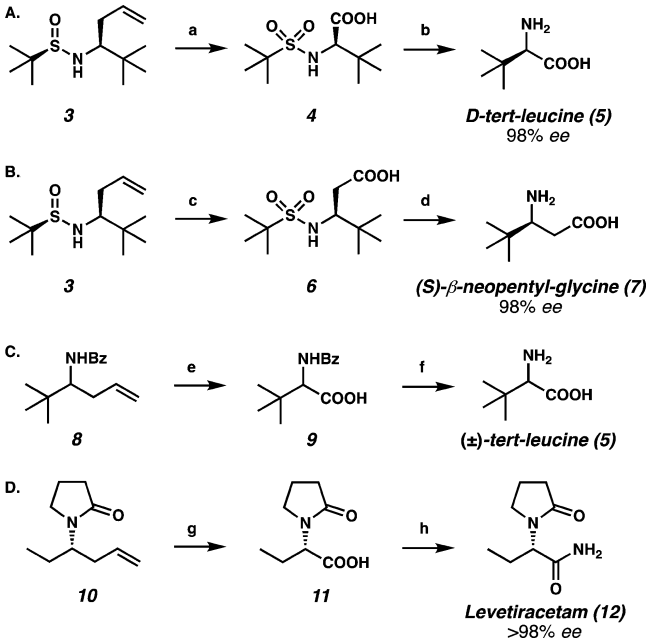
Figure 2. Identified ruthenium catalysts for olefin isomerization/oxidation sequences: an *in situ* formed ruthenium-hydride complex **1b** derived from Grubbs second-generation catalyst (**1a**) and Grotjahn's catalyst (**2**).

was highly chemoselective for alkene isomerization and displayed good conversion (>90%) without noticeable side reactions. Moreover, we discovered that the *in situ* formed Ru−H complex[17] **1b**, after solvent exchange, can be oxidized with $NaIO_4$ to an oxidized ruthenium species,[18] which is capable of catalyzing subsequent oxidation reactions (e.g., oxidative cleavage of alkenes, Scheme 2).[19] It has to be reinforced at this point that we do not add a new external ruthenium source for the second step. Instead, the crude transition metal catalyst from the previous isomerization step is modified *in situ* and reused for the catalytic oxidation reactions. Moreover, the only operation between the two steps is evaporation of the solvent from the isomerization reaction (toluene for **1a**, acetone for **2**) followed by dissolution of the crude reaction mixture in the solvent mixture used for oxidation (CCl_4, MeCN, H_2O).

Even though $NaIO_4$-mediated oxidations of ruthenium alkylidene complexes and their use in sequential and tandem catalysis[19b,20] have been described previously (e.g., RCM/dihydroxylation),[21] the modification and multiple use[13] of ruthenium-hydride complex[17] **1b** (derived from precatalyst **1a**) or ruthenium phosphine-imidazole complex[22] **2** in an isomerization/oxidation sequence was not known, until now (Figure 2).

Hence, chiral homoallylic amine **3**, which was readily synthesized via diastereoselective allylation of Ellman's sulfinimine,[5e] was subjected to the optimized conditions using Grubbs catalyst **1a**, giving the isomerized alkene in 98% conversion (Scheme 3A). After oxidation of the crude catalyst,

Scheme 3[a]



[a]Reagents and conditions: (a) 1. Grubbs **1a** (5 mol %), VTMS, toluene, reflux, 21 h, 98% conv., *E*/*Z* 4.4:1; 2. $NaIO_4$, CCl_4, MeCN, H_2O, 23°C, 2.5 d, 72% yield over 2 steps, 99% ee; (b) 1. TfOH, CH_2Cl_2, 0 °C, 2.5 h; 2. IEC, 96% yield, 98% ee; (c) $RuCl_3{\cdot}H_2O$ (5 mol %), $NaIO_4$, CCl_4, MeCN, H_2O, 23 °C, 16 h, 93% yield; (d) 1. TfOH, CH_2Cl_2, 0 °C → 23°C, 2 d; (2) IEC, 91% yield, 98% ee; (e) 1. Grubbs **1a** (5 mol %), VTMS, toluene, 128°C, 16 h, 97% conv., *E*/*Z* 4:1; 2. $NaIO_4$, CCl_4, MeCN, H_2O, 23 °C, 22 h, 88% yield over 2 steps; (f) 1. 4 M aq. HCl, MeOH, reflux, 24 h; 2. IEC, 57% yield; (g) 1. Grubbs **1a** (5 mol %), VTMS, toluene, 128°C, 18 h, 92% conv., *E*/*Z* 4.5:1; 2. $NaIO_4$, CCl_4, MeCN, H_2O, 23°C, 24 h, 62% yield over 2 steps; (h) $ClCO_2Et$, NEt_3, THF, then NH_4OH, 0 °C → 23 °C, 19 h, 67% yield, >98% ee. IEC = ion exchange chromatography, VTMS = vinyloxy trimethylsilane.

an alkene cleavage/sulfinamide oxidation duet[23] took place, furnishing Bus-protected[24] D-*tert*-leucine (**4**) in 72% yield over two steps, notably without racemization (99% ee). The Bus-protected amino acid **4** can be employed directly for a peptide coupling as reported by Hanessian,[24] or the Bus group is readily cleaved under acidic conditions to afford D-*tert*-leucine (**5**) in 96% yield (98% ee) after ion exchange chromatography.

Alternatively, by leaving out the olefin isomerization, sulfinamide **3** was subjected to a similar alkene cleavage/sulfinamide oxidation sequence with a catalytic amount of $RuCl_3$ hydrate, giving Bus-protected *β*-amino acid **6** in 93% yield (Scheme 3B). After deprotection and ion exchange chromatography, (*S*)-*β*-neopentylglycine (**7**) was obtained in 91% yield and 98% ee. Benzoyl-protected amine **8**, which is accessible in enantiopure form using Schaus' allylboration,[25] performed equally well in our sequential ruthenium catalysis, affording carboxylic acid **9** in 88% yield over two steps

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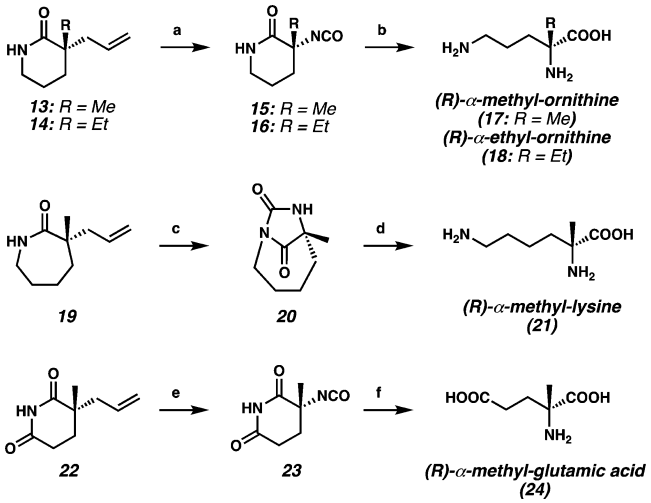
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(Scheme 3C). Benzoyl deprotection with aqueous HCl in methanol provided racemic *tert*-leucine (**5**) in 57% yield.

The sequential ruthenium catalysis was then used for an enantioselective total synthesis of levetiracetam (**12**), the active pharmaceutical ingredient of the antiepileptic medicine Keppra (Scheme 3D).[26] The synthesis commenced from homoallylic amide **10**, which was prepared in four steps from commercially available propionaldehyde and Ellman's auxiliary[5e] (see the Supporting Information for details). Sequential ruthenium catalysis of alkene **10** with Grubbs catalyst **1a** provided access to carboxylic acid **11** in 62% yield over two steps. Amidation of **11** was achieved via the corresponding mixed anhydride and reaction with ammonium hydroxide as described previously by Sánchez.[27] Levetiracetam (**12**) was isolated in 67% yield (>98% ee) and, after one recrystallization, was enriched to excellent enantiopurity (>99.9% ee).

We next applied our sequential ruthenium catalysis conditions to α-quaternary lactams (Scheme 4), which were

Scheme 4[a]



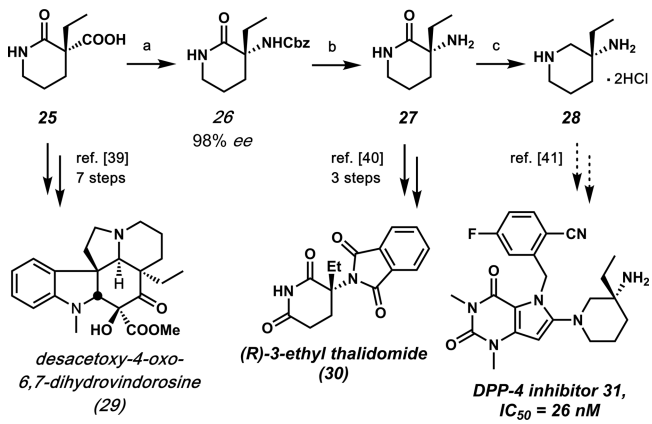
[a]Reagents and conditions: (a) **15**: 1. Grubbs **1a** (5 mol %), VTMS, toluene, 130 °C, 18 h, 88% conv.; 2. $NaIO_4$, CCl_4, MeCN, H_2O, 23 °C; 3. DPPA, NEt_3, MeCN, 0 °C → 65 °C, 3 h, 27% yield over 3 steps; **16**: 1. Grubbs **1a** (5 mol %), VTMS, toluene, 125 °C, 16 h, 96% conv. or Grotjahn **2** (2 mol %), acetone-d_6, 70 °C, 63 h, 95% conv.; 2. $NaIO_4$, CCl_4, MeCN, H_2O, 23 °C, 3. DPPA, NEt_3, MeCN, 0 °C → 65 °C, 47% yield over 3 steps (with **1a**) and 52% yield over 3 steps (with **2**); (b) **17**: 1. 4 M aq. HCl, 1,4-dioxane, 120 °C, 12 h; 2. IEC, 61% yield; **18**: 1. 2 M aq. HCl, THF, reflux, 24 h; 2. IEC, 95% yield; (c) 1. Grubbs **1a** (5 mol %), VTMS, toluene, 129 °C, 21 h, 96% conv., 2. $NaIO_4$, CCl_4, MeCN, H_2O, 23 °C, 24 h; 3. DPPA, NEt_3, MeCN, 0 °C → 65 °C, 3 h, 65% yield over 3 steps; (d) 1. 4 M aq. HCl, dioxane, reflux, 18 h; 2. IEC, 92% yield; (e) 1. Grubbs **1a** (5 mol %), VTMS, toluene, 129 °C, 21 h, 93% conv.; 2. $NaIO_4$, CCl_4, MeCN, H_2O, 23 °C, 25 h; 3. DPPA, NEt_3, MeCN, 0 °C → 65 °C, 3 h, 34% yield over 3 steps; (f) 1. 4 M aq. HCl, dioxane, reflux, 18 h; 2. IEC, 99% yield. DPPA = diphenyl phosphoryl azide, IEC = ion exchange chromatography, VTMS = vinyloxy trimethylsilane.

readily available in enantiopure form using palladium-catalyzed decarboxylative allylic alkylation.[8a,28] The unprotected methyl- and ethyl-substituted lactams **13** and **14** were treated with a catalytic amount of Grubbs catalyst **1a**, and the internal alkene was subsequently cleaved to give the crude carboxylic acids. A Curtius rearrangement[29] then furnished isocyanates **15** and **16** in 27% and 47% yield over three steps, respectively.[30] Likewise, we found that 2 mol % of Grotjahn's catalyst[22] (**2**, Figure 2) worked equally well[31] for the ruthenium-catalyzed isomerization/oxidation sequence of lactam **14** to give, after Curtius rearrangement, isocyanate **16** in a comparable 52% yield over three steps.[32] Hydrolysis of the isocyanate and the amide bond of **15** and **16** were achieved under acidic conditions to give access to enantiopure (*R*)-α-methylornithine[33] (**17**) and (*R*)-α-ethylornithine[34] (**18**) in 61% and 95% yield, respectively. The latter has been synthesized for the first time as a single enantiomer.[34] Biologically, both α-alkyl ornithine analogues are known to be ornithine decarboxylase inhibitors.[33a,34]

Treatment of caprolactam **19** and glutarimide **22** with catalyst **1a** under our optimized conditions gave, after Curtius rearrangement, hydantoin **20** and isocyanate **23** in 65% and 34% yield over three steps, respectively. Anti-Bredt bicycle[35−37] **20** results from an intramolecular cyclization of the lactam NH to the isocyanate. Its structure was unambiguously confirmed by X-ray crystallography (see the Supporting Information). Subsequent hydrolysis of **20** and **23** with aqueous HCl furnished (*R*)-α-methyllysine[33d] (**21**) and (*R*)-α-methylglutamic acid[33c,38] (**24**), respectively, in excellent yields (92% and 99%). Given the recent availability of α-quaternary lactams and imides,[28] it is possible to envision the synthesis of a wide range of α-substituted amino acid derivatives for a multitude of applications.

The enantioenriched carboxylic acid **25**, obtained by our Ru-catalyzed isomerization/oxidation method on lactam **14** (Scheme 4), not only is an intermediate in Padwa's racemic synthesis of desacetoxy-4-oxo-6,7-dihydrovindorosine[39] (**29**) but can also be used for the synthesis of Cbz-protected α-amino lactam **26** (98% ee) by trapping the intermediate isocyanate **16** with benzyl alcohol following the Curtius rearrangement (Scheme 5). Hydrogenolysis of the Cbz group gave amino lactam **27** in quantitative yield, which renders Knabe's racemic synthesis of 3-ethyl thalidomide[40] (**30**) enantioselective. Reduction of lactam **27** with $LiAlH_4$, followed by precipitation as the bishydrochloride salt, furnished chiral diamine **28** in 89% yield. The racemic, mono-Boc-protected version of **28** was used recently by

Scheme 5[a]



[a]Reagents and conditions: (a) DPPA, NEt_3, DCE, 23 °C → reflux, 5 h, then BnOH, reflux, 38 h, 29% yield, 98% ee; (b) H_2, Pd/C, MeOH, 23 °C, 4 h, >99% yield; (c) $LiAlH_4$, THF, 0 °C → reflux, 24 h, then HCl/dioxane, 89% yield. DCE = 1,2-dichloroethane, DPPA= diphenyl phosphoryl azide.

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Nishio et al.[41] for the synthesis of dipeptidyl peptidase IV (DPP-4) inhibitors.

CONCLUSIONS

In summary, we have developed a highly efficient ruthenium-catalyzed isomerization/oxidation sequence, which enabled the syntheses of challenging unnatural amino acids such as D-*tert*-leucine (**5**), (*S*)-*β*-neopentylglycine (**7**), (*R*)-*α*-methyl- and ethylornithine (**17** and **18**), (*R*)-*α*-methyllysine (**21**), and (*R*)-*α*-methylglutamic acid (**24**). The reaction sequence performs well with not only ruthenium-hydride complex **1b** (derived from Grubbs catalyst **1a**) but also the less common Grotjahn catalyst **2**. We found that both isomerization catalysts **1b** and **2** can be used to perform one or several subsequent oxidation steps after $NaIO_4$ treatment of the crude reaction mixtures. To demonstrate the utility of our method, we have completed an enantioselective total synthesis of the antiepileptic drug levetiracetam (**12**) and enantioselective formal syntheses of vindorosine derivative **29** and of (*R*)-3-ethyl thalidomide (**30**). Given the importance and ubiquity of the amino acid subunit in organic chemistry, we believe that our method will inspire many creative permutations and applications. Further usages of the method are currently under investigation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b08496.

Experimental procedures and characterization data (PDF)
Crystallographic information files (CIF)
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Notes

The authors declare no competing financial interest.

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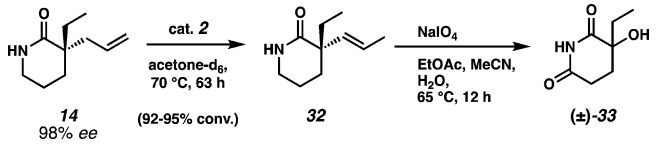
(31) The major difference between the reactivity of catalyst **1b** and **2** is that ruthenium hydride complex **1b** is highly selective for the isomerization of just one position to give the 2-ene product. In contrast, catalyst **2** is more reactive and less selective, which may lead to overisomerization for substrates containing a proton in position 4 of the allyl group such as for **3**, **8**, and **10**. This difference in reactivity is in agreement with a lower catalyst loading used for **2** (2 mol %) compared to **1b** (5 mol %). Since we had large quantities of **1a** available in our lab and catalyst **2** was rather expensive at the time (commercially available from Strem Chemicals and abcr GmbH, CAS 930601-66-4), we preferred to use **1a** for Scheme 4. However, similar yields are expected for both catalysts **1a** and **2** to those we have shown for substrate **14**.
(32) When we used forcing conditions for the second step with catalyst **2** (5 and 10 mol %), we observed a "lactam oxidation/alkene cleavage/decarboxylation/hydroxylation" reaction quartet for **32**. The tertiary alcohol **33** was isolated in 16% and 32% yield over two steps, respectively. Unfortunately, the reaction led to a racemic product.



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