Enzyme- and Ruthenium-Catalyzed Enantioselective Transformation of \(\alpha\)-Allenic Alcohols into 2,3-Dihydrofurans

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Abstract: An efficient one-pot method for the enzyme- and ruthenium-catalyzed enantioselective transformation of \(\alpha\)-allenic alcohols into 2,3-dihydrofurans has been developed. The method involves an enzymatic kinetic resolution and a subsequent ruthenium-catalyzed cycloisomerization, which provides 2,3-dihydrofurans with excellent enantioselectivity (up to \(> 99\% \text{ ee}\)). A ruthenium carbene species was proposed as a key intermediate in the cycloisomerization.

Allenes, a class of compounds with a unique substructure of two cumulative carbon–carbon double bonds, have been proven to be powerful building blocks for the construction of complicated skeletons.\cite{1,2} Thus, much attention has been focused on the transition metal-catalyzed cyclization of allenes\cite{3-5} with a nucleophilic functionality to synthesize a variety of potentially useful heterocycles.\cite{6-10} For example, \(\alpha\)-allenic alcohols with a sterogenic center provide ready access to chiral oxocycles. In the past few decades, a number of methods have been reported for the synthesis of chiral \(\alpha\)-allenic alcohols.\cite{7,10,11} However, these methods either require stoichiometric chiral reagents or a complicated chiral ligand, the multiple-step synthesis of which would limit their practical application. Therefore, new methodologies for efficient access to optically pure \(\alpha\)-allenic alcohols with broad compatibility and excellent enantioselectivity are still highly desired.

Enzymatic kinetic resolution (KR)\cite{12} of racemates is an efficient and powerful method to produce enantiomerically enriched compounds.\cite{13a} Enzymatic KR would give excellent enantioselectivity for those substrates that conform to the Kazlauskas rule\cite{13b} (Figure 1a), such as aryl-substituted propargylic alcohols (Figure 1b). However, enzymatic transformations of \(\alpha\)-allenic alcohols are still challenging, as the allene unit did not fit well as the medium-sized group into the active site of typical lipases, thus leading to low enantioselectivity (Figure 1c).\cite{11} Therefore, synthetically efficient enzymatic kinetic resolution of chiral \(\alpha\)-allenic alcohols is still a problem.\cite{14} Furthermore, dynamic kinetic resolution (DKR), which could overcome the theoretical maximum yield of 50\% of KR, would enable the desired enantiomer to be obtained in up to 100\% yield by coupling of the KR with a suitable racemization reaction (Scheme 1).\cite{15} However, we were surprised to find that the racemization catalyst C1 (Scheme 2) did not racemize allenic alcohols, but instead promoted their cyclization in an unexpected way. On the basis of this observation, we developed a one-pot process for the enantioselective synthesis of 2-substituted 2,3-dihydrofurans with the highest ee values observed for these compounds among all existing methods.

We screened a series of biocatalysts for the enantioselective transacylation of allenic alcohols 1 in organic solvents (for details, see Table S1 in the Supporting Information). CALA gave relatively low enantioselectivity and a low

\[\text{Scheme 1. Envisioned dynamic kinetic resolution (DKR) of }\alpha\text{-allenic alcohols and observed outcome.}\]
reaction rate. By control of the reaction time and temperature with substrate 1a, the CALB family (CALB wild type and a CALB mutant\(^{[16]}\)) afforded moderate \(E\) values (ranging from 32 to 44 depending on the variant and the solid support). To our delight, lipase PS on different solid supports displayed excellent enantioselectivity; IL1-PS (IL1-supported lipase PS) showed the best enantioselectivity and highest reaction rate. After this preliminary screening (see Table S1) we next investigated the substrate scope for the enzymatic kinetic resolution under the optimal reaction conditions. Although the \(E\) values were low for the two starting materials (rac)-1c and (rac)-1l (with 2-methoxyphenyl and cyclohexyl R substituents), probably owing to steric hindrance, IL1-PS showed excellent enantioselectivity for a wide range of substrates, in which the allene was tolerated as the medium-sized group (see Table S2). The calculated \(E\) values for these substrates ranged from 100 to 780.

With a high \(E\) value, both the allenic alcohol and the allenic acetate can be obtained with high \(ee\) values in the KR. The KR of (rac)-1f under optimal conditions gave (S)-1f with 99.9% \(ee\) in 43% yield and (R)-3f with 95.2% \(ee\) in 47% yield within 8 h [Eq. (1)].

![Scheme 1. Ruthenium-catalyzed cycloisomerization of (rac)-1.][1]

\[
\begin{align*}
\text{(rac)-1f} & \quad \xrightarrow{\text{IL1-PS, Na}_{2}C_{6}H_{5}} \quad \text{isopropenyl acetate, toluene, 50 °C, 8 h} \\
\xrightarrow{\text{(S)-1f}} & \quad \text{pure (99.9% ee)} \\
\xrightarrow{\text{(R)-3f}} & \quad \text{pure (95.2% ee)}
\end{align*}
\]

Having established this highly enantioselective KR method, we attempted to develop a DKR method by combining the KR with the Shvo catalyst (Cl)\(^{[17,18]}\). On the basis of previous research within our research group on the dynamic kinetic resolution (DKR)\(^{[19]}\) of secondary alcohols, in which biocatalysts are combined with a transition-metal catalyst, we tested racemization catalysts C1 and C2 (Scheme 2) with 1-phenylbuta-2,3-dien-1-ol ((rac)-1a) as the standard substrate. When (rac)-1a was treated with catalyst C1, isopropenyl acetate, and IL1-PS in the presence of \(\text{Na}_{2}C_{6}H_{5}\) in toluene at 70 °C overnight, the desired product was not observed. Surprisingly, the cyclized product 2a (see Table 1) was obtained in 83% yield as a single product. In contrast, catalyst C2 was inactive toward the allenic alcohol (rac)-1a.

![Scheme 2. Ruthenium-based racemization catalysts.][2]

Table 1: Ruthenium-catalyzed cycloisomerization of (rac)-1.\(^{[2]}\)

| Entry | R       | \(t\) [h] | Yield of 2 [%][\(\text{ee}\)] |
|-------|---------|----------|-----------------------------|
| 1     | Ph      | 1.5      | 83 (rac)-2a                 |
| 2     | 4-MeC_{6}H_{4} | 1.5 | 85 (rac)-2b                 |
| 3     | 2-MeO-C_{6}H_{4} | 1.5 | 88 (rac)-2c                 |
| 4     | 3-MeO-C_{6}H_{4} | 1.5 | 91 (rac)-2d                 |
| 5     | 4-MeO-C_{6}H_{4} | 1.5 | 77 (rac)-2e                 |
| 6     | 4-BrC_{6}H_{4} | 2      | 93 (rac)-2f                 |
| 7     | 4-ClC_{6}H_{4} | 2      | 92 (rac)-2g                 |
| 8     | 4-FC_{6}H_{4} | 2      | 84 (rac)-2h                 |
| 9     | 4-CF_{3}C_{6}H_{4} | 4    | 85 (rac)-2i                 |
| 10    | 2-Np    | 4      | 95 (rac)-2j                 |
| 11    | Bn      | 1.5    | 90 (rac)-2k                 |
| 12    | cyclohexyl | 1.5  | 90 (rac)-2l                 |

[a] The starting alcohol (rac)-1 (0.5 mmol) was dissolved in toluene (1 mL) in the presence of the Shvo catalyst C1 (2 mol%). [b] Yield of the isolated product. Bn = benzyl, Np = naphthyl.

We next set out to optimize the reaction conditions for the ruthenium-catalyzed cyclization with C1 by using (rac)-1a as the substrate (for details, see Table S3). Toluene, THF, DCE, acetone, dioxane, MeOH, and MeCN were tested as the solvent, and all gave (rac)-2a as a single product. The best result was found with toluene, which afforded (rac)-2a in 83% yield (Table 1, entry 1). The reaction still proceeded well with a catalyst loading of 2 mol%.

Under the optimal reaction conditions, we next investigated the scope of the cycloisomerization of allenic alcohols (rac)-1. A range of substituted 1-aryl buta-2,3-dien-1-ols were examined: Derivatives substituted with p-Me, o-MeO, m-MeO, p-MeO, p-Br, p-Cl, and p-F groups all reacted smoothly to afford the corresponding products (rac)-2b-h as the only product in excellent yields (Table 1, entries 2–8). However, substrates bearing an electron-deficient substituent, such as p-CF_{3} (substrate (rac)-1j) and 2-naphthyl (substrate (rac)-1j), required a longer reaction time (4 h vs. 1.5 h; Table 1, entries 9 and 10). The cycloisomerization reaction also proceeded well to give 2k and 2l in excellent yields when the R substituent was an alkyl group, such as benzyl (substrate (rac)-1k) or cyclohexyl (substrate (rac)-1l).

We next studied the cyclization of optically pure (S)-1a. Since catalyst C1 is utilized as a racemization catalyst in the DKR of secondary alcohols and primary amines, a drop in the \(ee\) value may occur during the cyclization. When optically pure (S)-1a (obtained by KR with IL1-PS) was treated with catalyst C1 (5 mol%) at 70 °C for 16 h, (S)-2a was obtained with 97.3% \(ee\) [Eq. (2)]. This result indicates that the cycloisomerization is about two orders of magnitude faster than racemization, which means that the configuration of the
The stereogenic center will be maintained in the C1-catalyzed cyclization.

With these results in hand, we designed an enantioselective one-pot synthesis of 2,3-dihydrofurans by combining the enzymatic kinetic resolution with C1-catalyzed cycloisomerization (Scheme 3). To our delight, for substrates with good E values in KR, the cycloisomerization products (S)-2 were obtained in 37–45% yield with excellent asymmetric induction (97.5–99.9% ee). Furthermore, even substrate (rac)-1c, which underwent slow KR with low selectivity, was converted into (S)-2c in 29% yield with 99.6% ee with a longer reaction time.

To demonstrate the synthetic utility of the products, we conducted an epoxide-formation–opening reaction to introduce two new chiral centers (Scheme 4). Compound 4, which can be isolated from its diastereomers, was produced in 65% yield without loss of optical purity (97.5% ee). Compound 4 can be used in the synthesis of optically pure (−)-3-deoxyisoaltholactone, the enantiomer of a natural product, by an existing method.[19]

We further studied the mechanism of this ruthenium-catalyzed cycloisomerization. It was first investigated whether 2,5-dihydrofuran 5 could be an intermediate in this reaction (Scheme 5). Compound 5, synthesized by a known method,[20] was heated to 70°C for 4 h in the presence of catalyst C1 (2 mol%) in toluene. Surprisingly, instead of 2f, an unsaturated ketone 6 was formed in quantitative yield. This observation suggests that 5 is not an intermediate in the catalytic cycle.

In an effort to gain deeper insight into the reaction mechanism, we performed deuterium-labeling experiments. The reaction was carried out with [D1]1f as the starting material in the presence of catalyst C1 (2 mol%) in toluene at 70°C for 2 h (Scheme 6a). Compound 2fa was formed with...
full conversion with a combined amount of 0.7 deuterium atoms in the position of the two allylic hydrogen atoms X¹ + X² and 19% deuterium incorporation at the vinylic position X³. A cyclization reaction of [D₄]1f was carried out under the same reaction conditions to give 2fb. To our surprise, a very similar deuterium distribution at the allylic position (X¹ + X²) and vinylic position X³ was observed (Scheme 6b). The only difference was that instead of 0% deuterium incorporation at the vinylic position X³ as in 2fa, 100% deuterium incorporation was found at the X³ position of 2fb. The reaction of [D₄]1f (Scheme 6c) afforded product 2fc, which had about twice the amount of deuterium in positions X¹ + X² and X³ as compared to the previous products 2fa and 2fb.

On the basis of the deuterium-labeling experiments, we propose a possible mechanism for the cycloisomerization of substituted 2,3-allen-1-ols (Scheme 7; see Scheme S2 in the Supporting Information). Coordination of the terminal C=O bond of 1 to Ru would form int-1, and subsequent ring closure of int-1 would give a vinyl–ruthenium intermediate int-2. Rearrangement of int-2 would give the key intermediate ruthenium carbene int-3. Protonation of int-3 to give int-4 and subsequent deprotonation at the CH₂O position would produce int-5. The reaction of int-4 to give int-5 is believed to be irreversible, since the cyclization of [D₄]1f to 2fb (Scheme 6b) led to 100% deuterium incorporation at the vinylic position X³. The equilibrium between int-4 and int-3 will lead to the observed deuterium content in the allylic (X¹ + X²) position of the product, which reflects the D/H ratio in the solvent. The much lower deuterium content in the vinylic position X³ is due to a kinetic isotope effect (kD/kH) in the protonation of int-5, since this step is irreversible.

In conclusion, we have developed a novel synthesis of 2-substituted 2,3-dihydrofurans from readily available allene alcohols through a ruthenium-catalyzed cycloisomerization. On the basis of this transformation, a one-pot enantioselective process combining KR and cycloisomerization was established. Oxygen-containing heterocycles were synthesized under mild reaction conditions with good functional-group tolerance. The products obtained can be further transformed into a variety of important derivatives. This method should be attractive for the pharmaceutical industry. A ruthenium carbene int-4 is proposed as a key intermediate of the cyclization.

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[1] a) H. F. Schuster, G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, 1984; b) S. Patai, *The Chemistry of Ketenes, Allenes, and Related Compounds*, Part I, Wiley, New York, 1980.

[2] For reviews, see: c) C. S. Adams, C. D. Weatherly, E. G. Burke, J. M. Schomaker, *Chem. Soc. Rev. 2014*, 43, 3136; d) T. Lechel, F. Pfrengle, H.-U. Reissig, R. Zimmer, *ChemCatChem 2013*, 5, 2100; e) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev. 2000*, 100, 3067; d) J. A. Marshall, *Chem. Rev. 2000*, 100, 3163; e) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res. 2001*, 34, 535; f) R. W. Bates, V. Satcharoen, *Chem. Soc. Rev. 2002*, 31, 12; g) J. Ye, S. Ma, *Org. Chem. Front. 2014*, 1, 1210; h) L.-L. Wei, H. Xiong, R. P. Huang, *Acc. Chem. Res. 2003*, 36, 773; i) P. Rivera-Fuentes, F. Diederich, *Angew. Chem. Int. Ed. 2012*, 51, 2818; *Angew. Chem. 2012*, 124, 2872; j) S. Ma, *Acc. Chem. Res. 2009*, 42, 1679; k) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Soc. Rev. 2010*, 39, 783; l) S. Ma, *Aldrichimica Acta 2007*, 40, 91; m) M. Jeganmohan, C.-H. Cheng, *Chem. Commun. 2008*, 3011.

[3] a) S. K. Hashmi, *Angew. Chem. Int. Ed. 2000*, 39, 3590; *Angew. Chem. 2000*, 112, 3737; o) L. K. Sydnes, *Chem. Rev. 2003*, 103, 1133; p) A. Hoffmann-Röder, N. Krause, *Angew. Chem. Int. Ed. 2002*, 41, 2933; *Angew. Chem. 2002*, 114, 3057; q) C. Aubert, L. Fensterbank, P. García, M. Malacria, A. Simonneau, *Chem. Rev. 2011*, 111, 1954; r) N. Krause, C. Winter, *Chem. Rev. 2011*, 111, 1994; s) F. López, J. L. Mascaró, *Chem. Eur. J. 2011*, 17, 418; t) S. Yu, S. Ma, *Angew. Chem. Int. Ed. 2012*, 51, 3074; *Angew. Chem. 2012*, 124, 3128; u) S. Yu, S. Ma, *Chem. Commun. 2011*, 47, 5384; v) S. Ma, *Acc. Chem. Res. 2003*, 36, 701; w) J. Ye, S. Ma, *Acc. Chem. Res. 2014*, 47, 989; x) S. Ma, *Chem. Rev. 2005*, 105, 2829.

[4] For Ag, see: a) M. Harmata, *Silver in Organic Chemistry*, Wiley, New York, 2010

[5] For Pd, see: a) J. Piera, K. Nähr, J.-E. Bäckvall, *Angew. Chem. Int. Ed. 2006*, 45, 6914; *Angew. Chem. 2006*, 118, 7068; b) A. K. Persson, J.-E. Bäckvall, *Angew. Chem. Int. Ed. 2010*, 49, 4624; *Angew. Chem. 2010*, 122, 4728; c) Y. Deng, T. Bartholomezyk, J.-E. Bäckvall, *Angew. Chem. Int. Ed. 2013*, 52, 6283; *Angew. Chem. 2013*, 125, 6403; d) C. Zhu, B. Yang, T.
Jiang, J.-E. Bäckvall, Angew. Chem. Int. Ed. 2015, 54, 9066; Angew. Chem. 2015, 127, 9194; c) C. Zhu, X. Zhang, X. Lian, S. Ma, Angew. Chem. Int. Ed. 2012, 51, 7817; Angew. Chem. 2012, 124, 7937; f) C. Zhu, S. Ma, Angew. Chem. Int. Ed. 2013, 52, 1542; g) C. Zhu, S. Ma, Adv. Synth. Catal. 2014, 356, 3987; h) C. Zhu, S. Ma, Angew. Chem. Int. Ed. 2014, 53, 13532; Angew. Chem. 2014, 126, 13750; i) C. Zhu, B. Yang, J.-E. Bäckvall, J. Am. Chem. Soc. 2015, 137, 11868; k) C. Zhu, B. Yang, Y. Qiu, J.-E. Bäckvall, Chem. Eur. J. 2016, 22, 2939.

[5] For Au, see: a) D. J. Gorin, F. D. Toste, Nature 2007, 446, 395; b) Y. Qiu, D. Ma, C. Fu, S. Ma, Tetrahedron 2013, 69, 6305; c) Y. Qiu, J. Zhou, J. Li, C. Fu, Y. Guo, H. Wang, S. Ma, Chem. Eur. J. 2015, 21, 15939.

[6] S. Ma, S. Zhao, J. Am. Chem. Soc. 1999, 121, 7943.

[7] a) Y. Wang, K. Zhang, R. Hong, J. Am. Chem. Soc. 2012, 134, 4096; b) S. Ma, W. Gao, J. Org. Chem. 2002, 67, 6104.

[8] a) E. Yoneda, T. Kaneko, S. Zhang, K. Onitsuka, S. Takahashi, Org. Lett. 2000, 2, 441; b) E. Yoneda, S. Zhang, D. Zhao, K. Onitsuka, S. Takahashi, J. Org. Chem. 2003, 68, 8571.

[9] a) Y. Blum, Y. Shvo, Isr. J. Chem. 1984, 24, 144; b) Y. Shvo, D. Czarkie, Y. Rahamim, D. F. Chodosh, J. Am. Chem. Soc. 1986, 108, 7400.

[10] a) R. Karvembu, R. Prabhakaran, K. Natarajan, Coord. Chem. Rev. 2005, 249, 911; b) B. L. Conley, M. K. Pennington-Boggio, E. Boz, T. J. Williams, Chem. Rev. 2010, 110, 2294; c) J. S. M. Samec, J. E. Bäckvall, Encyclopedia of Reagents for Organic Synthesis, 2nd ed., Wiley Interscience, 2009.

[11] a) E. Yoneda, T. Kaneko, S. Zhang, K. Onitsuka, S. Takahashi, Org. Lett. 2000, 2, 441; b) E. Yoneda, S. Zhang, D. Zhao, K. Onitsuka, S. Takahashi, J. Org. Chem. 2003, 68, 8571.

[12] a) Y. Blum, Y. Shvo, Isr. J. Chem. 1984, 24, 144; b) Y. Shvo, D. Czarkie, Y. Rahamim, D. F. Chodosh, J. Am. Chem. Soc. 1986, 108, 7400.

[13] a) R. Karvembu, R. Prabhakaran, K. Natarajan, Coord. Chem. Rev. 2005, 249, 911; b) B. L. Conley, M. K. Pennington-Boggio, E. Boz, T. J. Williams, Chem. Rev. 2010, 110, 2294; c) J. S. M. Samec, J. E. Bäckvall, Encyclopedia of Reagents for Organic Synthesis, 2nd ed., Wiley Interscience, 2009.

[14] After the completion of this study, a KR of allenic alcohols was reported that gave good enantioselectivity in 1–5 days: W. Li, Z. Lin, L. Chen, X. Tian, Y. Wang, S.-H. Huang, R. Hong, Tetrahedron Lett. 2016, 57, 603.

[15] After the completion of this study, a KR of allenic alcohols was reported that gave good enantioselectivity in 1–5 days: W. Li, Z. Lin, L. Chen, X. Tian, Y. Wang, S.-H. Huang, R. Hong, Tetrahedron Lett. 2016, 57, 603.

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