Highly Enantioselective Synthesis of 3-Substituted γ-Butenolides by Palladium-Catalyzed Kinetic Resolution of Unsymmetrical Allyl Acetates**

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The Pd-catalyzed asymmetric allylic alkylation (AAA) holds a prominent position among the most versatile methods for C–C bond formation that are widely applied in natural product synthesis.[1] This transformation typically features broad functional group tolerance and excellent regio- and enantioselectivity.[2-3] In particular, Pd-catalyzed kinetic resolutions of symmetrical allylic substrates and dynamic product synthesis.[3,4] This transformation typically features substrates with silyl enol ethers as nucleophiles.

Scheme 1. Pd-catalyzed asymmetric allylic alkylation of unsymmetrical substrates with silyl enol ethers.

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**[**] Selection of reaction parameters.

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[a] 2 equiv of 2a used. [b] 1 equiv of 2a used. [c] The conversion and ratio of regioisomers were determined by GC analysis with n-dodecane as the internal standard. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Absolute configuration was assigned by comparison of the sign of optical rotation with published values.

Herein, we present the Pd-catalyzed kinetic resolution of 1,3-disubstituted unsymmetrical allylic substrates with non-stabilized silyl enol ethers as nucleophiles, which provides a highly regio- and enantioselective synthesis of 3-substituted γ-butenoled. The γ-butyrolactone skeleton is present in more than 13000 natural products, which have attracted considerable attention because of the range of important biological activities associated with this class of compounds.[13] As part of our program to develop catalytic enantioselective methods to access optically active γ-butenolides and lactones,[12] we envisioned the possibility of using 2-trimethylsilyloxyfuran (TMSOF)[13] as nucleophile in a Pd-catalyzed AAA reaction.

Initially, we examined the allylic substitution of carbonate 1a by utilizing TMSOF as nucleophile and a chiral Pd catalyst based on Trost Ligand L1 (Table 1, entry 1). The 3-substituted product 3 and 5-substituted product 4 were obtained in a 2:1 ratio and in 36% ee for product 3 (Table 1, entry 1). Using a lower temperature (0°C), the ee value only slightly increased (49% ee, Table 1, entry 2). With tert-butyl carbonate as the leaving group, the regioselectivity shifted in favor of the formation of the 5-substituted product (3/4 = 1:2, Table 1,
entry 3). Remarkably, when the simple allylic acetate 1c was used, 80% conversion was reached at room temperature and both the regio- and enantioselectivity were significantly enhanced (3/4 = 5:1, 78% ee, Table 1, entry 4).

Encouraged by these results, the reaction of allyl acetate 1c was carried out at 0°C instead of room temperature. In this case, the reaction ceased at 53% conversion but provided enantiomerically pure recovered (S)-1c through kinetic resolution of the substrate. Furthermore, in this Pd-catalyzed allylic alkylation, 3c is the only reaction product that is obtained in near-perfect chemo-, regio- (3/4 > 99:1) and enantioselectivity (99% ee). Notably, the reaction could also be carried out with one equivalent of 2a to give the same results (Table 1, entry 6).[14]

Remarkably, when the kinetic resolution of 1c was performed under the optimized conditions shown in Table 1, entry 6, but over a longer reaction time, the transformation virtually ceased at 50% conversion and 1c was recovered in 99% ee, which illustrates a near-perfect selectivity in the kinetic resolution as well (Figure 1). It is also remarkable that the reaction proceeds with complete regioslectivity towards the formation of 3c (Table 1, entry 5) instead of 4c, which would be expected based on the common reactivity pattern of TMSOF.[15] Only very few examples are known in which TMSOF reacts at the C3 position.[13]

To establish unequivocally the absolute stereochemistry of 3c, it was determined by X-ray diffraction analysis on a single crystal of the resulting chromium complex (see the Supporting Information).[17]

The scope of the reaction was examined under the optimized conditions (Table 1, entry 6) for a range of racemic allylic acetates (Table 2). Generally, most of the products were obtained with excellent ee values and very high S factors. When unsymmetrical acetates 1d and 1e with electron-withdrawing or -donating groups at the para position of phenyl ring, respectively, were investigated, excellent regio- and enantioselectivity was maintained (Table 2, entries 2 and 3). The ortho-methoxy-substituted substrate 1f also led to excellent enantioselectivity both in recovered 1f and the product 3f (Table 2, entry 4).

We next turned our attention to dialkyl substituted allylic acetates for the kinetic resolution. Although the recovered allylic acetates had a slightly lower enantiomeric excess than the aryl-substituted allylic acetates, the 3-substituted products 3g and 3h were obtained in 99% ee and with excellent regioselectivity, both with respect to butenolide and unsymmetrical disubstituted allyl fragments (Table 2, entries 5 and 6). It is important to note that the reaction proceeds very well with both aromatic- and alkyl-substituted unsymmetrical substrates and provides impressive selectivity in both cases.

The allylation of symmetrical, dimethyl-substituted substrate 1i shows only a slight decrease in enantioselectivity, both for recovered 1i and the product 3i (Table 2, entry 7).[18] Furthermore, treatment of racemic cyclohexenyl acetate 1j under the optimized conditions gave the corresponding product 3j almost exclusively with an excellent ee value, and 1j was also recovered in 99% ee (Table 2, entry 8). In contrast, racemic 1,3-diphenylallyl acetate 1k provided the 3-substituted product 3k with full conversion in 87% ee and with poor regioselectivity (Table 2, entry 9). The reaction of

![Figure 1](image1.png)

**Figure 1.** Kinetic resolution of 1c (see Table 1, entry 6).

![Graph1](image2.png)

![Graph2](image3.png)

**Table 2:** Substrate scope for kinetic resolution.[a]

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[a] Reaction conditions: 1/2a/[R,R]-L1/[Pd2(dba)3]·CHCl3 (100:100:15:5), 1 in CH2Cl2 (0.175 mL) at 0°C, 0.5 h for addition of 1 by syringe pump. [b] Conversion and the ratio of regioisomers were determined by GC analysis with n-dodecane as the internal standard. [c] Determined by HPLC and GC analyses on chiral stationary phases. [d] Yield of isolated product. [e] No trace of S,Z product was detected. [f] S = kS/kR = In[(1–C/100) (1–ee/100)]/ln[(1–C/100) (1+ee/100)] (C = conversion; ee = enantiomeric excess of recovered substrate). [g] The absolute configuration of 3c was assigned based on the X-ray analysis of a single crystal. [h] The reaction was performed at room temperature with 2 equiv of 2a.
this common model substrate for allylic alkylation does not follow the kinetic resolution pathway.\(^{[19]}\)

To gain further insight into the key structural parameters and mechanistic features of the reaction, different methyl-substituted 2-silyloxyfurans were investigated (Schemes 2 and 3). When the 3 position of the furan ring was blocked by a methyl group, the alkylation reaction went exclusively through attack at the 5-position, which afforded a 4:1 mixture of diastereomers and the major isomer in 86% ee (Scheme 2).

A moderate enantiomeric excess (46% ee) was obtained for recovered 1c.

A remarkable shift in selectivity was obtained when we carried out the reaction with allyl acetate 1l, that is, the regioisomer of 1c (Scheme 3). Instead of exclusive formation of 3c in 99% ee, surprisingly, the reaction only provided a 9:1 diastereomeric mixture of 4l, in which the 3-substituted product was not detected. Furthermore, the recovered starting material was obtained as a nearly racemic mixture.

To further understand the mechanism of the reaction, we carried out model studies and DFT calculations.\(^{[20]}\) Based on the conformation of Pd/(R,R)-L1 reported by Lloyd-Jones and co-workers,\(^{[21]}\) we performed a conformational search on the Pd–olefin complexes of both enantiomers of 1c (see the Supporting Information). These results indicate that the acetate carbonyl group of enantiomer (R)-1c forms a hydrogen bond with the amide hydrogen of ligand L1 on the concave side of catalyst Pd/(R,R)-L1 (Figure 2a), whereas the same stabilization for enantiomer (S)-1c is absent (Figure 2b). The energy difference of about 11 kcal mol\(^{-1}\) between these (η\(^2\)-allyl)Pd complexes would explain the result of the kinetic resolution in which the R substrate has been completely consumed. A similar result was reported by Lloyd-Jones and coworkers.\(^{[21]}\) In the neutral pre-ionization of h\(^2\)-cyclic ester complexes, they found that the acetate carbonyl group of the S enantiomer accepts a hydrogen bond from the amide hydrogen on the concave side of the Pd complex, whereas no corresponding stabilization is available for the R enantiomer. This result suggests that only one enantiomer of the acetate can be selectively ionized because of the stabilization of the leaving acetate anion through hydrogen bonding.

Furthermore, the DFT calculations showed that the most stable product of the reaction is the one that is obtained from allylic alkylation at the 3 position on the furanone ring (which bears a conjugated double bond) with the R configuration. We also determined that there is hydrogen bond between the oxygen of the carbonyl group of the furanone product 3c and the amide hydrogen on the concave side of the Pd complex (Figure 2c).

It has been described, for the Pd-catalyzed allylic alkylation of malonate derivatives with this particular ligand (R,R)-L1, that the hydrogen bonding interaction between the enolate oxygen atom and the amide hydrogen atom can direct the enolate carbon atom to the closest enantioface of the η\(^2\)-allyl complex.\(^{[21]}\) We envision that hydrogen bonding (also

**Scheme 2.** Allylic alkylation of substituted 2-silyloxyfuran 2b. TMS = trimethylsilyl.

**Scheme 3.** Allylic alkylation of 1c and 1l with 2a.

**Figure 2.** B3LYP structures of a) Pd/(R,R)-L1/(R)-1c, b) Pd/(R,R)-L1/(S)-1c, and c) the 3-substituted product 3c coordinated with complex Pd/(R,R)-L1 (arrow indicates hydrogen bond).
present in the final product, see Figure 2c) between the oxygen anion of the incoming enolate and the amide hydrogen atom of the catalyst (with which the carbonyl oxygen atom of the acetate leaving group interacts) controls the stereoselectivity of the nucleophilic attack (Scheme 4). That is, the removal of the acetate leaving group and the delivery of the nucleophile proceeds by an identical enantioface selection pathway. The key to the selectivity is a selective acetate—enolate exchange, which suggests that the whole process takes place with net retention of configuration, which is in perfect agreement with the obtained experimental results. This result is in full accordance with the proposal of Lloyd-Jones and co-workers,[21] in which they identify that the hydrogen-bond interaction of one N—H unit in the Pd-coordinated complex can substantially accelerate both ionization and nucleophilic attack. Moreover, this hydrogen bond pre-orient the allyl unit for ionization and also directs the orientation of nucleophile delivery.[22] Most probably, a subsequent olefin isomerization of the butenolide also takes place in the Pd complex, which gives rise to the final product.[23]

In summary, we have developed a Pd-catalyzed kinetic resolution of 1,3-disubstituted unsymmetrical allylic acetates and a concomitant allylic alkylation by using silyl enol ethers as nucleophiles, to access important 3-substituted γ-butenolides. The reaction proceeds under mild conditions and provides the desired product with excellent chemo-, regio-, and enantioselectivity. Preliminary studies indicate that hydrogen-bonding interactions with the chiral ligand might play a key role in the control of the regio- and enantioselectivity. Further studies on the unusual reactivity of TMSOF, the mechanistic implications of our findings, and extension of this highly selective catalytic method are ongoing.

**Experimental Section**

General procedures for Pd-catalyzed kinetic resolution (Table 2): A solution of the ligand (0.0525 mmol, 38 mg) in CH₂Cl₂ (1 mL) was added to a dry Schlenk tube that contained [Pd₂(dba)₄]CHCl₃ (0.0175 mmol, 18 mg). After stirring at room temperature for 15 min, a solution of TMSOF (0.35 mmol, 60 µL) in CH₂Cl₂ (0.5 mL) was added dropwise. After the mixture had been stirred for another 15 min, a solution of the allylic acetate (0.35 mmol) and n-dodecane (30 µL, internal standard) in CH₂Cl₂ (0.5 mL) were added by syringe pump over 0.5 h at 0°C. The progress of the reaction was monitored by GC and GC-MS. After the completion of the reaction, the reaction solvent was evaporated under vacuum. The crude product was purified by flash chromatography on silica gel by using different mixtures of pentane/Et₂O as eluents. Toluene/Et₂O 95:5 was used as the eluent for TLC to distinguish between the regioisomers.

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[14] When ligand (S,S)-Li1 was used, the recovered acetate and product were obtained with opposite configurations with similar conversion and ee values.


[17] CCDC 857213 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
The yield was low probably because of the high volatility of the recovered allylic acetate and the product.

This result was in accordance with the finding that sterically more encumbered substrates often gave lower enantioselectivity with the Pd-L1 catalyst: G. Helmchen, U. Kazmaier, S. Forster, Catalytic Asymmetric Synthesis, 3rd ed. (Ed.: I. Ojima), Wiley-VCH, New York, 2010, pp. 497–641.


It is still not clear when the double bond migration take place. Isomerization of butenolides promoted by hydrogen bonding has been described, see: Y. Wu, R. P. Singh, L. Deng, J. Am. Chem. Soc. 2011, 133, 12458–12461.