



Thermodynamic equilibration in Pd(0)-catalyzed interconversion of highly constrained [2.1.2] bicyclic lactones: its mechanistic investigation

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ABSTRACT

Mechanistic study on the stereoselective construction of [2.1.2] bicyclic lactone skeleton via Pd(0)-catalyzed intramolecular allylic alkylation was described. The observed excellent stereoselectivity is likely due to Pd(0)-catalyzed equilibration of highly strained [2.1.2] bicyclic lactone framework via π - σ - π isomerization of π -allylpalladium complex. An efficient synthetic route to allylic carbonate as a requisite cyclization precursor has also been developed by employing a sequence of ring-closing metathesis, followed by epoxidation/desilylation of the resulting substituted oxasilepene intermediate.

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Recently, we have reported highly stereoselective construction of unique bicyclic lactones via intramolecular Pd(0)-catalyzed allylic alkylation.^{1,2} The [2.1.2] or [2.2.1] bicyclic lactones could be utilized as excellent equivalents of contra thermodynamic *trans*-substituted cyclopentanes, which have importantly been utilized for total syntheses of bioactive natural products.^{2,3} These applications implied high utility of the bicyclic lactone architectures (Fig. 1).

On the way of our synthetic studies toward (+)-brefeldin A, however, unexpectedly poor diastereoselectivity (dr 2:1) was

observed in conversion of **7** as a diastereomeric mixture to the corresponding bicyclic lactone **8** (Eq. 1).⁴ We could solve the problem by cyclization of the diastereomerically pure allylic carbonate **7**^{3c,4} or the highly diastereoselective route of **1** to **2**, followed by desulfonylation and subsequent cross metathesis of bicyclic lactone **3** with siloxyheptene.^{3d} In spite of the development of successful route, the observed diastereoselectivity was quite disappointing because the rapid π - σ - π isomerization of π -allylpalladium complex was anticipated for the exclusive formation of the desired bicyclic lactone **8**.

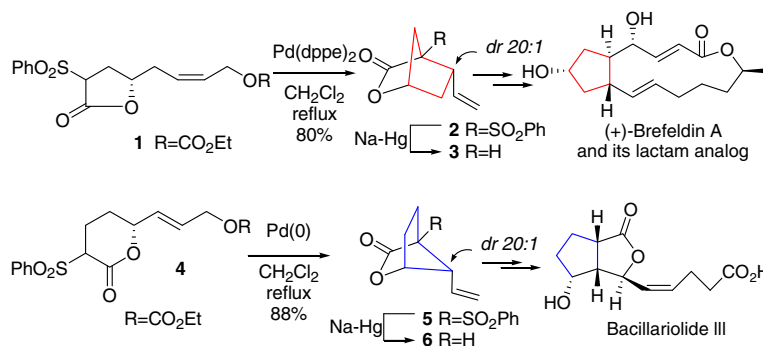


Figure 1. Stereoselective synthesis and applications of bicyclic lactones.

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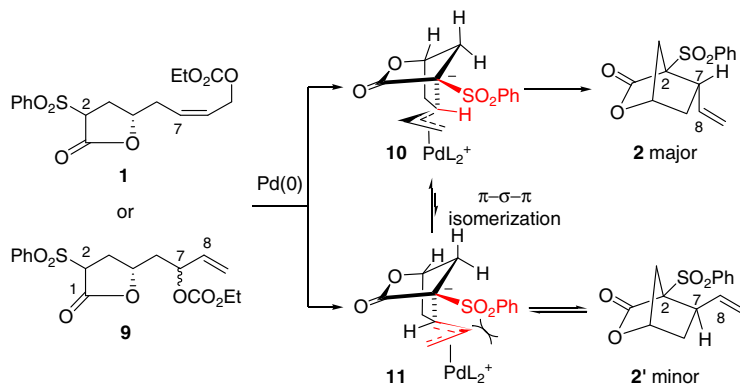
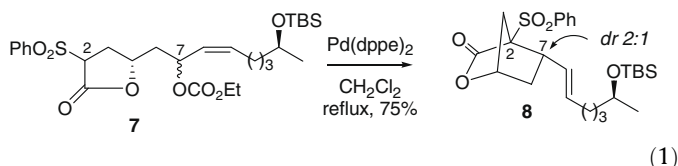


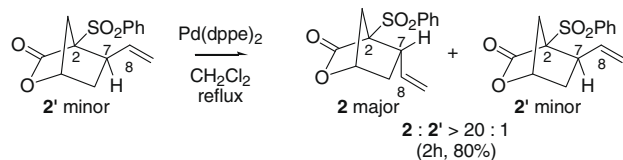
Figure 2. Plausible pathway for the highly diastereoselective cyclization.



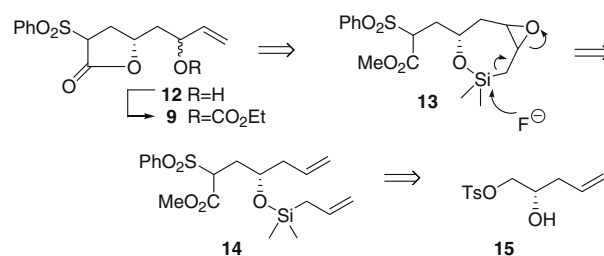
Thus, investigation on the origin of diastereoselectivity was focused on π - σ - π isomerization of π -allylpalladium complex because the diastereoselectivity seems to be complicated by the disubstituted olefinic system^{3c} rather than the stereochemistry at C7. In particular, we were interested in reversibility of the C2–C7 single bond formation in the highly constrained bicyclic system such as **2** on the basis of Pd(0)-catalyzed C–C bond cleavage/formation sequence,⁵ which would reinforce high diastereoselectivity of the cyclization process for [2.1.2] bicyclic lactone **2** through C2–C7 cleavage of the thermodynamically less favorable product **2'** followed by π - σ - π isomerization (Fig. 2).^{1,6,7}

Based on the hypothesis, we examined Pd(0)-catalyzed equilibration⁷ between **2** and **2'**. At first, chromatographically separable diastereomers **2** and **2'** were prepared by stereoselective cyclization of precursor **1**,¹ and interconversion between the major diastereomer **2** and the minor diastereomer **2'** was carried out (Scheme 1). Upon treatment of the minor product **2'** with Pd(dppe)₂ in refluxing CH₂Cl₂ for 2 h, the major product **2** was obtained exclusively (ca. 20:1) as expected. It was obvious that combination of the highly strained bicyclic framework and the relatively less hindered terminal olefin was responsible for the reversible C(sp₃)–C(sp₃) bond cleavage/formation in the presence of Pd(0) catalyst⁵ (Scheme 1). It is noteworthy that the thermodynamic equilibration of C–C single bond cleavage/formation in bicyclic systems such as **2'** has not been reported yet, although a few examples of C–C single bond cleavage under similar conditions were reported for cyclopropane, cyclobutane, or sterically encumbered quaternary carbon skeleton to the best of our knowledge.⁵

Confirming the interconversion of the [2.1.2] bicyclic lactones **2** and **2'**, we turned our attention to thermodynamic equilibration of the Pd(0)-catalyzed allylic alkylation of allylic carbonate **9** as a diastereomeric mixture. It was anticipated that the presence of a less hindered terminal olefin in the cyclization precursor **9** would not complicate the Pd(0)-catalyzed equilibration between **2** and **2'**.



Scheme 1. Pd(0)-catalyzed equilibration of **2** and **2'**.

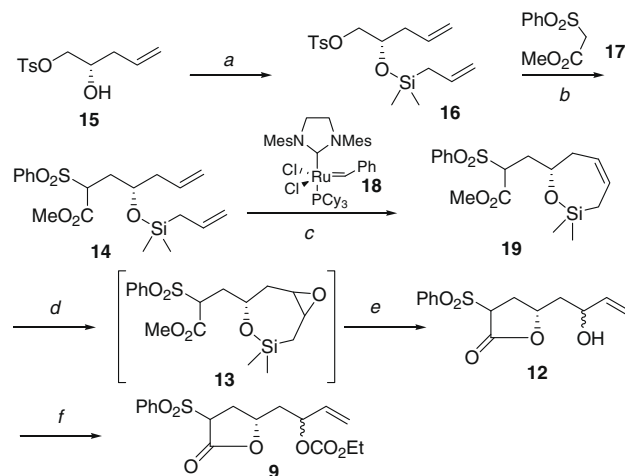


Scheme 2. Retrosynthesis for the monosubstituted allylic carbonate **9**.

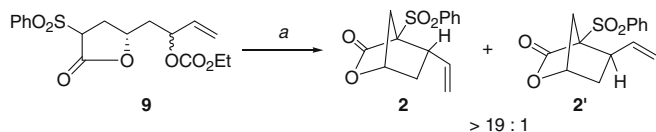
Accordingly, the exclusive formation of **2** as a thermodynamically favored product was also expected regardless of the stereochemistry of the secondary alcohol at C7 of **9** (Fig. 2).

Thus, an efficient synthesis of allylic carbonate **9** possessing terminal olefin was planned as outlined in Scheme 2.⁸ It was envisioned that allylic alcohol **12** could be conveniently synthesized through a sequence of desilylation and ring opening⁹ of epoxide **13**, followed by subsequent lactone formation. It was also anticipated that the unstable epoxide **13** could be prepared via ring-closing metathesis of diene **14**¹⁰ followed by epoxidation of the resulting olefin. Diene **14** would be readily prepared from the known homoallylic alcohol **15**¹¹ by allylsilylation and alkylation of benzenesulfonylacetate.

As shown in Scheme 3, the alcohol **15** was silylated and the resulting tosylate **16** was subjected to enolate alkylation conditions of NaH in DMF to afford silyl ether **14** in a yield of



Scheme 3. Reagents and conditions (a) allyldimethylsilyl chloride, imidazole, DMF, 0 °C to rt, 91%; (b) **17**, NaH, DMF, 0 °C to 80 °C, 72 h, 82%; (c) 1 mol % **18**, CH₂Cl₂, 40 °C, 20 min, 95%; (d) mCPBA, NaHCO₃, CH₂Cl₂, –40 °C, 72 h; (e) TBAF, THF, 0 °C, 5 h, 99%; (f) ClCO₂Et, pyridine, CH₂Cl₂, 0 °C to rt, 6 h, 94%.



Scheme 4. Reagents and conditions: (a) 5 mol % Pd(dppe)₂, CH₂Cl₂, 40 °C, 2 h, 80%.

75% for two steps. Diene **14** was treated with Grubbs' 2nd generation catalyst **18**¹² to provide oxasilepene **19** in a yield of 95%. Fortunately, dimeric or olefin-isomerized byproduct was not observed. Epoxidation of oxasilepene **19** with mCPBA afforded the unstable epoxide **13**, which was directly treated with TBAF to give the requisite allylic alcohol **12** in 2:1 diastereomeric ratio in nearly quantitative yield for two steps.¹³ The diastereomeric mixture **12** was converted to the corresponding carbonate **9** by standard ethoxycarbonylation.³ Finally, we were able to secure the desired cyclization precursor **9** in more than 10 g scale via an improved sequence of RCM, epoxidation, and then desilylation (65% from **15**).¹⁴

With allylic carbonate **9** possessing terminal olefin in hand, the key Pd(0)-catalyzed cyclization was carried out as shown in Scheme 4.¹⁵ Upon Pd(dppe)₂ treatment of **9** in CH₂Cl₂ at reflux condition, di-*cis*-substituted [2.1.2] bicyclic lactone **2** was obtained in more than 19:1 ratio, which was determined by isolation of each isomers. The result was in accordance with the cyclization result of our previous cyclization precursor **1**. This also supports Pd(0)-catalyzed thermodynamic equilibration of the highly strained [2.1.2] bicyclic lactone systems via sequential C–C bond cleavage, isomerization, and recyclization. The diastereoselectivity of this cyclization seems independent of the stereochemistry at allylic position of the allylic carbonate precursors unless the terminal olefinic carbon is substituted.

In summary, mechanistic aspect of highly stereoselective construction of the synthetically useful [2.1.2] bicyclic lactone system via Pd(0)-catalyzed intramolecular allylic alkylation was investigated. The excellent diastereoselectivity of the favorable [2.1.2] bicyclic lactone isomer is attributed to Pd(0)-catalyzed thermodynamic equilibration of each isomer via π - σ - π isomerization of π -allyl palladium complexes, which formed from either allylic carbonate or energetically less favorable [2.1.2] bicyclic lactone isomer. It is also noteworthy that Pd(0)-catalyzed cleavage of C–C single bond was observed for the synthetically useful and unique [2.1.2] bicyclic lactone system. We expect that mechanistic insight and evidences for thermodynamic equilibration could provide highly versatile synthetic applications.

Acknowledgments

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- Diastereomeric ratio at C7 was determined after desulfonylation of carbonate **9** using 6% Na-Hg, B(OH)₃ in MeOH.
- Synthesis of 9:** To a solution of **19** (70 mg, 0.19 mmol) in CH₂Cl₂ (2 mL), NaHCO₃ (48 mg, 0.57 mmol) was added and the reaction mixture was cooled to –40 °C. A solution of mCPBA (70 mg, 0.29 mmol) in CH₂Cl₂ (2 mL) was added and the reaction mixture was stirred for 3 days at the same temperature. After addition of aqueous NaHSO₃, the mixture was extracted with EtOAc twice. The combined organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was dissolved in THF (1 mL), and TBAF (1 mL, 1.0 M solution in THF) was added at 0 °C. After stirring for 5 h, the reaction was quenched with H₂O and the reaction mixture was extracted with EtOAc twice. The combined organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by chromatography on silica gel with a mixture of EtOAc and *n*-hexane (2:1) to afford 56 mg (99%) of allylic alcohol **12** for two steps as colorless oil. The allylic alcohol **12** was dissolved in CH₂Cl₂ (5 mL) and treated with pyridine (0.2 mL) and ClCO₂Et (0.1 mL) at 0 °C. The reaction was quenched with H₂O and the reaction mixture was extracted with EtOAc twice. The combined organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography on silica gel with a mixture of EtOAc and *n*-hexane (1:3) to afford 64 mg (94%) of allylic carbonate **9** as a colorless oil. ¹H NMR (CDCl₃, 300 MHz, mixture of four diastereomers) δ 7.93–7.85 (m, 2H), 7.69–7.63 (m, 1H), 7.57–7.51 (m, 2H), 5.80–5.68 (m, 1H), 5.37–5.16 (m, 3H), 4.82 and 4.58 (m, 1H) 4.18–4.10 (m, 2H), 4.08 and 4.00 (m, 1H), 3.10 and 2.79 (m, 1H), 2.55 and 2.30 (m, 1H), 2.08–1.92 (m, 1H), 1.28–1.16 (m, 4H) ppm; ¹³C NMR (CDCl₃, 125 MHz, mixture of four diastereomers) δ 170.7, 167.1, 166.9, 153.7, 136.4, 136.2, 134.7, 134.4, 134.3, 134.1, 133.9, 129.1, 129.0, 128.9, 128.7, 127.5, 118.9, 118.6, 117.7, 77.1, 76.3, 76.0, 74.9, 74.7, 74.5, 74.2, 74.1, 64.4, 64.3, 63.8, 63.4, 63.3, 60.0, 39.7, 39.3, 39.1, 29.8, 29.6, 28.9, 28.7, 20.7, 13.8 ppm; FT-IR (KBr) ν_{max} (cm^{–1}) 2984, 1778, 1744, 1448, 1372, 1324; LRMS (FAB) *m/z* 369 (M+H⁺); HRMS (FAB) calcd for C₁₇H₂₁O₅S 369.1008 (M+H⁺) found 369.1014.
- Pd(0)-assisted alkylation of allylic carbonate **9:** To a solution of allylic carbonate **9** (480 mg, 1.6 mmol) in CH₂Cl₂ (20 mL), a solution of Pd(dppe)₂ (73 mg, 5 mol %) in CH₂Cl₂ (5 mL) was added at 40 °C. After 2 h reflux, the reaction mixture was cooled to room temperature, diluted with Et₂O, and filtered by silica gel. The mixture was concentrated and the residue was purified by column chromatography on silica gel with a mixture of EtOAc and *n*-hexane (2:1) to afford 340 mg (76%) of the major adduct **2** and 17 mg (4%) of the minor adduct **2'**.