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Theoretical Investigation on Spiro-cyclisation of Maleimide and Sulfonamide Catalyzed by Pd(II) *via* Activated γ-C(sp3)−H to Spiro Pyrrolidine

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Abstract

Our DFT calculation provided the first theoretical investigation on Pd(OAc)2-catalyzed spiro-cyclisation of sulfonamide with maleimide. Initially, Pd(OAc)2 is coordinated with quinoline leading to first N-Pd bond. Subsequently, via coordination of sulfonamide to Pd, the second N-Pd bond is generated after liberation of first acetic acid AcOH. Then C-Pd bond is formed by activation of γ-C(sp3)−H bond during formation of key five-membered ring intermediate together with leaving of second AcOH. Further coordination with maleimide to Pd affords tensioned ternary ring, which converts into expanded seven-membered palladacycle through 1,2-migratory insertion. The β-hydride elimination and resulting coordination shift undergoes yielding six-membered ring. The final reductive elimination of it generates desired five-membered spiro pyrrolidine product and recovered Pd catalyst. Comparatively, the reductive elimination is speculated as rate-limiting for Pd(II)-mediated spiro-cyclisation of sulfonamide with maleimide producing spiro pyrrolidine.

Keywords: Pd(0)/Pd(II); Spirocyclization; Diastereomer; γ-C(sp3)−H Activation; Quinoline Ligand

Introduction

As key architecture in nature, the spiro cycle was attracted attention in medicinal and synthetic chemistry [1]. With distinct rigidity and restricted rotation at spiro centres, the assembly of spiro quaternary carbon centres with adjacent nitrogen in molecule makes them privileged moiety as chiral ligands. For example, Ghosh reported spirocyclization and dehydrogenation of succinimides via electrophilic C3-maleimidation in quinoxa-line catalyzed by Mn(I) [2]. Shennan discovered divergent approach to spirocyclic pyrrolidines [3]. Fang explored diastereo- and chemo selective cycloisomerization [4]. Mo researched chemical synthesis of spirocyclic indolines mediated by Cp2Fe [5]. Many efforts was focused on efficient method to spirocyclic core such as Shinde's Rhodium-(III)-catalyzed dehydrogenative annulation, Laru's Ru(II)-mediated switchable C–H alkylation, Sen's Cobalt-catalyzed C–H activation and Yuan's asymmetric [4+1] spirocyclization followed by C-H olefination [6-9]. In this field, the spiro cyclization is of special interest using maleimide as coupling partner for N-sulfonyl aromatic aldimine and benzamide [10].

In recent years, aliphatic C(sp3)–H bond functionalization remains a challenge due to inert metal–alkyl bonds. Although Ghosh developed merger of C(sp3)/(sp2)-H bond addition, Zhu explored high regioselective arylation carboxylate-directed of aliphatic acids catalysed by Pd, Naskar realized cyclization of substituted aliphatic carboxylic acids with allylic electrophiles [11-13], the great progress is Pd-catalyzed activation of β-C(sp3)–H bond forming aerobic oxidative spirodiamine scaffold using alkyl amides [14]. On the other hand, the inert C(sp3)–H bond activation is usually restricted to alkynylation, arylation, and carbonylation due to large bond dissociation energy such as Pd(II)-catalyzed β- and γ-C-(sp3)–H dienylation, direct alkynylation of free carboxylic acids, and assembly of tetrahy-droquinolines, 2-Benzazepines [15-17]. Thus, the activation of γ-C(sp3)–H after spiro annulation is still less explored in spite of ligand-enabled Pd catalysis in cross-coupling, γ-C(sp3)–H arylation, unsymmetrical diarylation and so on [18-20].

The peptides and proteins were chosen as substrates in stereoselective allylation catalyzed by transition-metal towards α,α-disubstituted amino acids with vicinal stereocenters [21]. Especially, Jeganmohan group has made many contributions in this context including C–H alkylation of vinylsilanes with sulfonamides catalyzed by Rh(II), palladium-catalyzed benzylic

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C–H alkylation of aromatic sulfonamides with maleimides [22-24]. Another breakthrough was Pd(OAc)2-catalyzed spiro-cyclisation of sulfonamide and maleimide via γ-C(sp3)–H bond activation [25]. Although desired spiro pyrrolidine was synthesized, how the site-selective functionalization was achieved for unactivated C(sp3)–H bond? What's the relation between pure enantiomeric separable diastereomers of product and Pd(0)/Pd(II) catalytic system? How five-membered nitrogen-containing spirocyclic was obtained in real reaction path?

Computational Details

The geometry was optimized with Gaussian 09 package at B3LYP/BSI level [26, 27]. The mixed basis set was denoted as BSI with LanL2DZ for Pd, 6-31G(d) for non-metal atoms [28-32]. Different singlet, multiplet states were clarified with B3LYP approach including Becke's three-parameter hybrid functional with Lee–Yang–Parr correction [33, 34]. Harmonic frequency calculations were carried out at B3LYP/BSI level to gain thermodynamic corrections and zero-point vibrational energy (ZPVE) at 378 K, 1 atm for each structure in dichloroethane (DCE). Using integral equation formalism polarizable continuum model (IEFPCM), the solvation-corrected free energies were obtained at B3LYP/6-311++G(d,p) (LanL2DZ for Pd) level on B3LYP/BSI-optimized geometries with Truhlar's "density" solvation model [35-37].

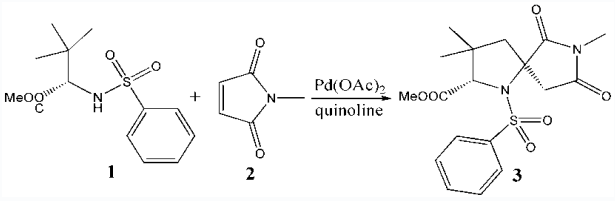
To characterize bonding orbital interactions and electronic properties, NBO procedure was performed with Natural bond orbital (NBO3.1) [38, 39]. Using Multiwfn_3.7_dev package [40], the wave function analysis was provided together by research on frontier molecular orbital (FMO).

Results and Discussion

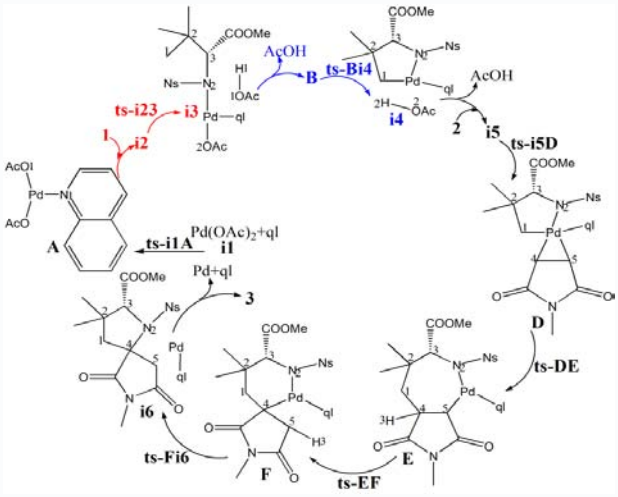
The mechanism was explored for Pd(OAc)2-catalyzed spiro-cyclisation of sulfonamide 1 with maleimide 2 leading to spiro pyrrolidine 3 (Scheme 1). As in Scheme 2, Pd(OAc)2 is initially coordinated with quinoline to produce complex A. Subsequently, complex B is generated via reaction of A with sulfonamide 1 after liberation of the first acetic acid AcOH (red arrow). Then C-Pd bond is formed by activating γ-C(sp3)–H bond during transformation of B into key five-membered intermediate C together with leaving of second AcOH (blue arrow). Further coordination with maleimide 2 affords D, which converts into seven-membered palladacycle intermediate E through 1,2-migratory insertion. E undergoes β-hydride elimination and coordination transfer to yield six-membered intermediate F, the reductive elimination of which generates desired five-membered spiro pyrrolidine 3.

Pd(OAc)2 coordination/AcOH liberation/γ-C(sp3)–H bond activation

Initially from complex i1 binding Pd(OAc)2 catalyst and quinoline, the coordination is accomplishd via ts-i1A in step 1 with



Scheme 1: $Pd(OAc)_2$-catalyzed spiro-cyclisation of sulfonamide **1** with maleimide **2** leading to spiro pyrrolidine **3**.



Scheme 2: Proposed reaction mechanism of $Pd(OAc)_2$-catalyzed spiro-cyclisation of **1** with **2** to access **3** (ql and Ns denote quinoline and $PhSO_2$). TS is named according to the two intermediates it connects.

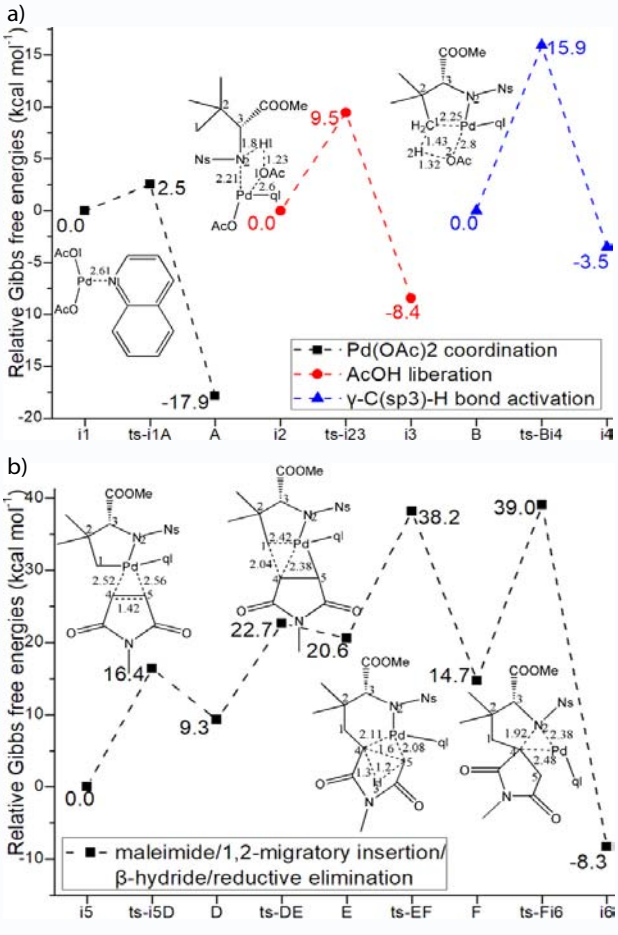


Figure 1: Relative free energy in solvent phase from complex (a) **i1**, **i2**, **B** (b) **i5**.

the activation energy of 2.5 kcal mol−1 exothermic slightly by -17.9 kcal mol−1 producing complex A (black dash line of Figure 1a). The transition vector is simple corresponding to approaching of Pd to N1 (2.61 Å). The low barrier suggests function of Pd(II).

Subsequently, the addition of sulfonamide 1 to A gives intermediate

Table 1: The activation energy of all steps.

TS	$\Delta G^{\neq}_{gas}$	$\Delta G^{\neq}_{sol}$
ts-i1A	2.9	2.5
ts-i23	9.6	9.5
ts-Bi4	17.7	15.9
ts-i5D	16.6	16.4
ts-DE	13.8	13.4
ts-EF	18.5	17.6
ts-Fi6	26.4	24.3

i2, from another coordinated Pd-N2 bond is formed via ts-i23 in step 2 with activation energy of 9.5 kcal mol−1 exothermic by -8.4 kcal mol−1 generating i3 (red dash line of Figure 1a). The transition vector not only includes N2 closing to Pd but previous proton H1 shifting from N2 to one OAc ligand of Pd namely N2···H1···O1 (2.21, 1.8, 1.23 Å) (Figure S1a). Therefore, after liberation of the first acetic acid AcOH, complex B is obtained involving activated substrate 1.

Then γ-C(sp3)−H bond activation occurs via ts-Bi4 in step 3 with activation energy of 15.9 kcal mol−1 exothermic by -3.5 kcal mol−1 delivering intermediate i4 (blue dash line of Figure 1a). From detailed atomic motion of transition vector, one proton on sp3 hybrid C1 forms second AcOH with another OAc ligand of Pd that is C1···H2···O2 (1.43, 1.32 Å) (Figure S1b). Meanwhile, nucleophilic attack C1 to Pd is achieved through C1···Pd (2.25 Å). Once typical C1-Pd bond is formed, B is transformed into key five-membered intermediate C without AcOH.

Maleimide insertion/1,2-migratory insertion/β-hydride elimination/reductive elimination

With C in hand, further coordination of it with maleimide 2 forms i5, which is taken as new starting point of next four steps. The insertion of 2 takes place via ts-i5D in step 4 with activation energy of 16.4 kcal mol−1 endothermic by 9.3 kcal mol−1 affording intermediate D. The transition vector corresponds to coordination of π electron on double bond C4=C5 to Pd forming C4···Pd, C5···Pd and stretching C4···C5 single bond in new tensioned ternary ring (2.52, 2.56, 1.42 Å) .

The next 1,2-migratory insertion proceeds via ts-DE in step 5 with activation energy of 13.4 kcal mol−1 endothermic by 20.6 kcal mol−1 realizing the expansion of five-membered D into more reactive seven-membered palladacycle intermediate E. The transition vector contains breaking of C1···Pd, C4···Pd and bonding of C1···C4 as well as strengthened C5-Pd (2.42, 2.38, 2.04 Å) (Figure S1c). Although the two steps just mentioned are both endothermic, the barriers are moderate demonstrating the reaction of two substrates is readily accessible under the assistance of Pd(II).

Then via ts-EF in step 6, E undergoes β-hydride elimination with activation energy of 17.6 kcal mol−1 yielding shrinking six-membered intermediate F with reduced relative energy by -5.9 kcal mol−1. The transition vector is complex comprising concerted proton transfer mode C4···H3···C5 and coordination shifting from C5 to C4 (1.3, 1.2 Å) (Figure S1d). With linkage of C4-Pd single bond and cleavage of C5···Pd, the stability of six-membered F is undoubtedly enhanced compared with seven-membered E.

At last, the reductive elimination of F happens via ts-Fi6 in step 7 with increased activation energy of 24.3 kcal mol−1 exothermic by -8.3 kcal mol−1 giving i6. The transition vector reveals squeezing of Pd between N2, C4 via N2···Pd, C4···Pd breakage and simultaneous N2···C4 connection (2.38, 2.48, 1.92 Å) (Figure S1e). The desired five-membered spiro pyrrolidine 3 is generated after accomplish of typical N2-C4 single bond and recovered Pd catalyst as retired mediator. Comparatively, this reductive elimination is rate-limiting for Pd(II)-catalyzed spiro-cyclisation producing spiro pyrrolidine.

Conclusions

The theoretical investigation was provided on Pd(OAc)2-catalyzed spiro-cyclisation of sulfonamide with maleimide. Pd(OAc)2 catalyst is initially coordinated with quinoline leading to first N-Pd bond. Subsequently, the second N-Pd bond is generated via coordination of sulfonamide to Pd after liberation of first acetic acid AcOH. Then C-Pd bond is formed by γ-C(sp3)−H bond activation during formation of key five-membered ring intermediate together with leaving of second AcOH. Further coordination with maleimide affords tensioned ternary ring, which converts into expanded seven-membered palladacycle through 1,2-migratory insertion. The β-hydride elimination and resulting coordination shift undergoes yielding six-membered ring, the reductive elimination of which generates recovered Pd catalyst and desired five-membered spiro pyrrolidine product. Comparatively, the reductive elimination is rate-limiting for Pd(II)-catalyzed spiro-cyclisation of sulfonamide with maleimide producing spiro pyrrolidine.

Electronic Supplementary Material

Supplementary data available: [Computation information and cartesian coordinates of stationary points; Calculated relative energies for the ZPE-corrected Gibbs free energies (ΔGgas), and Gibbs free energies (ΔGsol) for all species in solution phase at 378 K.]

Author Contributions

Conceptualization, Nan Lu; Methodology, Nan Lu; Software, Nan Lu; Validation, Nan Lu; Formal Analysis, Nan Lu; Investigation, Nan Lu; Resources, Nan Lu; Data Curation, Nan Lu; Writing-Original Draft Preparation, Nan Lu; Writing-Review & Editing, Nan Lu; Visualization, Nan Lu; Supervision, Nan Lu; Project Administration, Nan Lu. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest: The authors declare no conflict of interest.

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