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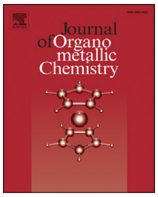

What factors cause the complete substrate-controlled selectivity in $Rh_2(Piv)_4$-catalyzed cycloadditions of 1,2,3-triazoles with isocyanates or isothiocyanates

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ABSTRACT

DFT studies on $Rh_2(Piv)_4$-catalyzed cycloadditions of 1,2,3-triazoles with isocyanates or isothiocyanates show that 1, 2, 3-triazoles undergo ring opening → coordination of $Rh_2(Piv)_4$ → dissociation of N_2 to give $Rh_2(Piv)_4$-azavinyl carbene, where $Rh_2(Piv)_4$ exerts a stabilizing effect on azavinyl carbene. The formed $Rh_2(Piv)_4$-azavinyl carbene prefers to nucleophilically cyclize with C=N bond of isocyanatobenzene to give the imidazolone, rather than C=O bond of isocyanatobenzene to give the oxazolimine. In comparison, $Rh_2(Piv)_4$-azavinyl carbene preferentially cyclize with C=S bond of isothiocyanatobenzene to give the thiazole, instead of C=N bond of isothiocyanatobenzene to give the thioimidazolone. The nucleophilic capacity follows C=S > C=N > C=O trend, which is the key selective origin of these reactions. The presence of $Rh_2(Piv)_4$ would help to form the carbene and to stabilize it via donating its *d*-electron into the azavinyl carbene, which is another selective origin of these reactions.

Introduction

The imidazolones and thiazoles are common building blocks of many bioactive molecules, such as anti-ulcer cimetidine [1], omeprazole [2], antiepileptics sodium phenytoin [3], beta-lactam antibiotics penicillins [4], antifungals drug clotrimazole [5] and antiparasitic drugs levamizole [6], and important intermediates of organic synthesis. Therefore, the constructions of imidazolones and thiazoles are very significant in organic and medicinal chemistry.

Over the past decades, various catalyzed methods involving transition metals have been developed to synthesize the imidazolone and thiazole derivatives. For instance, the imidazolone is constructed by $RuCl_2(PPh_3)_3$-catalyzed cyclization between N, N′-disubstituted ureas and vicinal-diols with 73% yield [7]. p-toluenesulfonic acid(TosOH)-catalyzed cyclization of 1,3-dimethylurea with 3-hydroxybutanone provides imidazolone derivative with 38% yield [8,9]. The imidazolone derivative is built by $(\eta^3\text{-}C_3H_5PdCl)_2$-catalyzed addition of aziridine with isocyanate in 98% yield [10]. 2-imidazolone derivatives can be achieved by silver triflate(AgOTf)-catalyzed cycloisomerization of isocyanates and propargylamines with 50–90% yield [11]. Tris(dibenzylideneacetone)dipalladium(Pd_2dba_3)-catalyzed cross-coupling of multicomponents generates the imidazolone derivatives with 80–90% yield [12]. $Rh_2(nC_7H_{15}COO)_4(Rh_2Oct_4)$-promoted N–H insertion of primary ureas and diazocarbonyls can provide imidazolone derivatives with 40–95% yield [13–15]. 5-functionalized thiazoles are synthesized by $Rh_2(NHCOC_3F_7)_4$-promoted addition of thiocarboxamides and carboxylates with 35–88% yield [16]. $ZnBr_2$-catalyzed cycloaddition of aziridines and isothiocyanates affords iminothiazolidines with 70–90% yield [17]. However, these reactions usually require harsh conditions or have relatively low selectivities.

Recently, $tBuCOORh_2$ ($Rh_2(Piv)_4$) is reported to catalyze cycloaddition of 1,2,3-triazoles with isocyanates to afford imidazolones rather than oxazolimines, while with isothiocyanates to completely provide thiazoles instead of thioimidazolones (Scheme 1) [18]. Noticeably, the difference of isocyanates and isothiocyanates only lies in one atom (oxygen or sulfur), and oxygen and sulfur are the elements in the same main group. Up to date few formation mechanism of imidazolone or thiazole are found in the literature [19,20]. Therefore, it is very significant to obtain an insight into

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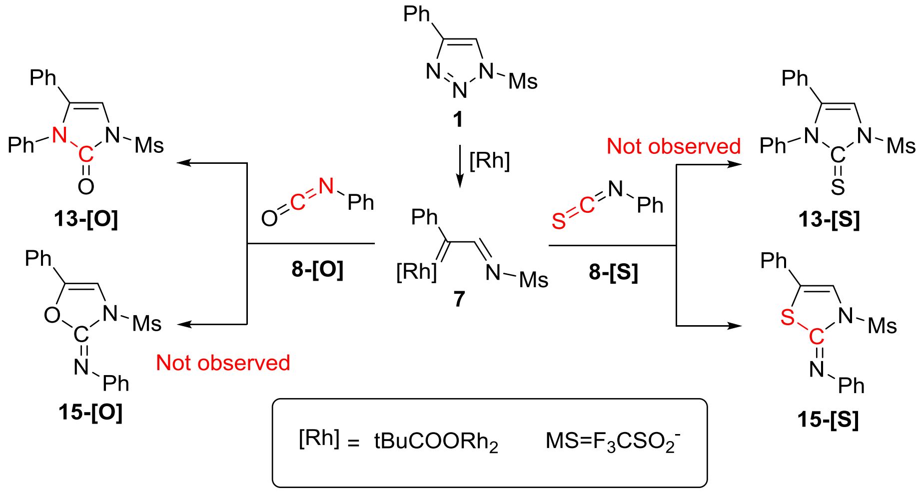

Scheme 1. $Rh_2(Piv)_4$-catalyzed cycloaddition of 1,2,3-triazoles and isocyanates or isothiocyanates.

$Rh_2(Piv)_4$-catalyzed cycloaddition of 1,2,3-triazoles with isocyanates or isothiocyanates, and illuminate the substrate-controlled selective origin of these reactions from molecular level.

Computational details

All the calculations were performed using Gaussian 09 program [21]. The Kohn-Sham density functional theory was solved with B3LYP functional [22]. The LANL2DZ [23,24] relativistic effective core potential (RECP) was used for Rh and S, and the LANL2DZ basis sets were modified, in which the secondary outer p functions of the standard LANL2DZ basis sets were replaced with optimized p functions, d-polarization functions ($\zeta_d = 0.503$) were added to S, and f-polarization($\zeta_f = 1.350$) functions were added to Rh [25,26]. 6-311G(d,p) basis set [27]was used for C, H, O, and N atoms in isocyanate, isothiocyanate, and 1,2,3-triazoles. The atoms of ligand (*t*BuCOO) away from the reaction regions were described with 6-31G basis set. Frequency analysis was carried out to verify the stationary points as minima or transition states and obtain free energy of each species. Intrinsic reaction coordinate(IRC) [28] calculations were used to judge whether the transition state connects the reactant and the product. Natural bond orbital (NBO) calculations [29–31] were used to understand how the changes in bonding and charge transfer affect the reaction. The influence of the solvent ($CHCl_3$) on the reaction was evaluated by using polarizable continuum model (PCM) [32,33] single-point calculation with the gas-phase optimized geometries. The molecular cavity was treated using the united atom Hartree-Fock(UAHF) parameterization. To confirm the equilibrium of basis set and obtain energy profile more accuracy, 6-311G(d,p) basis set was used for nonmetal, cc-pVTZ-pp was selected for Rh with effective core potential. Free energy of each species in solution was deemed as sum of the gas-phase free energy and the free energy of solvation. The energy difference between the lowest and highest points in the energy profile is closely related to the kinetics of the reaction [34]. But in this work, the geometries of each elementary step are mainly discussed, and to keep consistent, the energy changes of each elementary step are accordingly adopted.

Results and discussion

Based on the experiment [18], this work is divided into the formation of $Rh_2(Piv)_4$-azavinyl carbene and the cyclization of $Rh_2(Piv)_4$-azavinyl carbene with isocyanates or isothiocyanates.

The formation of $Rh_2(Piv)_4$-azavinyl carbene

The formation of $Rh_2(Piv)_4$-azavinyl carbene would involve three possible pathways (**Pathway I**, **Pathway II** and **Pathway III**). The optimized geometries and free energy profiles are given in Figs. 1 and 2.

Pathway I

From **1** to **TS2**, the ring opening of 1,2,3-triazole occurs with the N1–N2 distance stretching from 1.359 to 2.073 Å and ∠N2–N3–C4 increasing from 110.2° to 130.0°. NBO charges are decreased from −0.466 to −0.768 for N1 atom and from 0.087 to −0.009 for C4 atom, and increased from −0.061 to 0.119 for N2 atom and from −0.240 to −0.036 for N3 atom, suggesting that the electrons first flow from N2 to N1 atom (the heterolysis of N1–N2 bond) and are delocalized into C4 atom and N3 atom charges are simultaneously dispersed by N2 atom. In **3** NBO charges are calculated to be 0.101 for N3 atom and −0.058 for C4 atom, supporting **3** is a zwitterionic ring-opening intermediate. This process is endergonic by 4.8 kcal/mol with a free energy barrier of 16.3 kcal/mol.

When $Rh_2(Piv)_4$ coordinates to the ring-opening intermediate **3**, the N3–C4 bond is slightly weakened, which is favorable for the dissociation of N_2 to give carbene. The main reason is that $Rh_2(Piv)_4$ takes stabilizing effect on the formed carbene. The process from **3** to **5** is endergonic by 13.5 kcal/mol with a free energy barrier of 11.9 kcal/mol, which is very easy to occur.

From **5** to **TS6**, the dissociation of N_2 takes place with the N3–C4 distance lengthening from 1.348 to 1.759 Å and the N2–N3 distance shortening from 1.116 to 1.100 Å, and Rh1–Rh2 bond (2.413 → 2.450 Å) gradually elongates and the Rh1–C4 bond significantly shortens (2.572 → 2.193 Å). In **7**, the distance is 2.015 Å for Rh1–C4 bond and 1.448 Å for C4–C5 bond, and NBO population is $sp^{2.02}$ for C4 atom, showing that **7** has the character $Rh_2(Piv)_4$-azavinyl carbene [35]. This process is exergonic by 18.6 kcal/mol with a free energy barrier of 10.6 kcal/mol.

Pathway II

The ring opening of 1,2,3-triazoles is the same as that in pathway **I**, and thus is not discussed any more. The **3** → **TS6-noRh** → **7-noRh** process (Fig. S1), corresponding to the dissociation of N_2 from **3** without $Rh_2(Piv)_4$, is endergonic by 6.8 kcal/mol with a higher free energy barrier of 24.2 kcal/mol compared with the dissociation of N_2 (**5** → **TS6** → 7) in **Pathway I**. The coordination of $Rh_2(Piv)_4$ into carbene is exergonic by 11.9 kcal/mol.