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Divergent Reactivity in Pd-Catalyzed [3,3]-Sigmatropic Rearrangement of Allyloxy- and Propargyloxyindoles Revealed by Computation and Experiment

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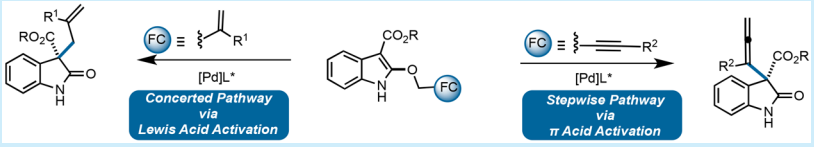
Supporting Information

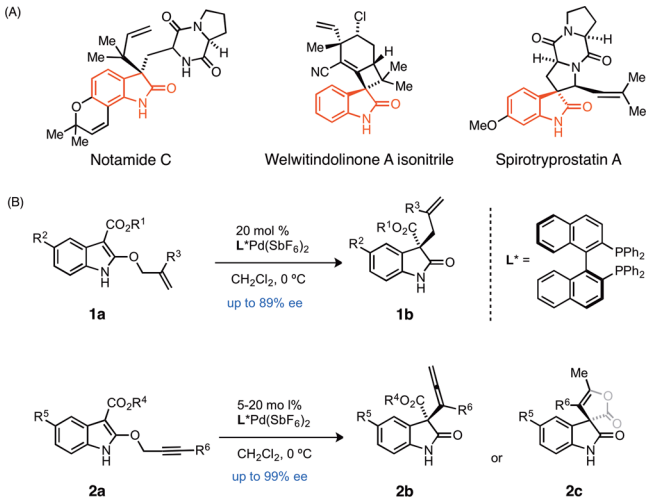


ABSTRACT: Detailed computational (DFT) studies of the palladium(II)-catalyzed Claisen rearrangement of 2-allyloxy- and propargyloxyindoles revealed an unexpected divergent mode of reactivity. Subsequent experimental kinetic isotope effects are in accord with the mechanism derived from the computations. The computational results led to the development of Pd(II)-catalyzed [3,3]-sigmatropic rearrangement of 3-aryl substituted 2-propargylindoles.

Sigmatropic shifts constitute an essential class of pericyclic reactions in organic chemistry.[1] Initially discovered by Cope and Hardy in 1940,[2] the thermal [3,3]-sigmatropic rearrangement of 1,5-dienes (e.g., Cope rearrangement) is the prototypical reaction of this class taught in undergraduate organic chemistry courses to showcase concerted (and stereospecific) σ- and π-bond reorganization.[3] Seminal work by Overman showed that palladium(II) chloride salts could catalyze the Cope rearrangement.[4] In 2012, Gagné and co-workers reported the first enantioselective variant using a chiral Au(I) catalyst.[5] More recently, Gleason and Kaldre reported the first organocatalytic Cope rearrangement using a novel chiral *N*-acyl diazepane as the catalyst.[6] In contrast to the Cope rearrangement, the [3,3]-sigmatropic rearrangement of allyl vinyl ethers (Claisen rearrangement) has been widely used in asymmetric catalysis and in the synthesis of complex natural products.[7,8] Our group became interested in utilizing a novel [3,3]-sigmatropic shift to access the C3-quarternary carbon oxyindole backbone found in many natural products (Scheme 1A). We discovered that axial chiral palladium(II) salts are able to catalyze the asymmetric [3,3]-sigmatropic rearrangement of 3-ester-substituted 2-allyloxy- and propargyloxyindoles with high yields and enantioselectivities (Scheme 1B).[9,10] Herein, we use a combined computational and experimental approach to elucidate the mechanism of these transformations. Surprisingly, DFT calculations and labeling experiments support a divergent mode of reactivity. Implications for rational reaction design are shown by engineering a new Pd(II)-catalyzed [3,3]-sigmatropic rearrangement of a system lacking the previously necessary chelating 3-ester group to generate 3-aryl-2-propargyloxyindoles.

We initiated our mechanistic studies by modeling the palladium(II)-catalyzed rearrangement of 3-methylester-2-allyloxyindole with $Pd(PH_3)_2Cl^+$ as a model catalyst (Figure 1).[11,12] As shown in Figure 1, palladium(II) complexation to 3-methylester-2-allyloxyindole can occur via Lewis acid type coordination to the carbonyl and ether (**1A**) or via π-coordination to the alkene moiety (**1A0**).[13] DFT calculations[14] show a strong preference (8.6 kcal/mol) for Lewis acid coordination, which leads to a concerted [3,3]-sigmatropic

Scheme 1. (A) Representative Natural Products Bearing the Oxyindole Backbone with a C3-Quaternary Stereocenter; (B) Enantioselective Palladium(II)-Catalyzed [3,3]-Sigmatropic Rearrangement of 2-Allyloxyindoles (Top) and 2-Propargyloxyindoles (Bottom)



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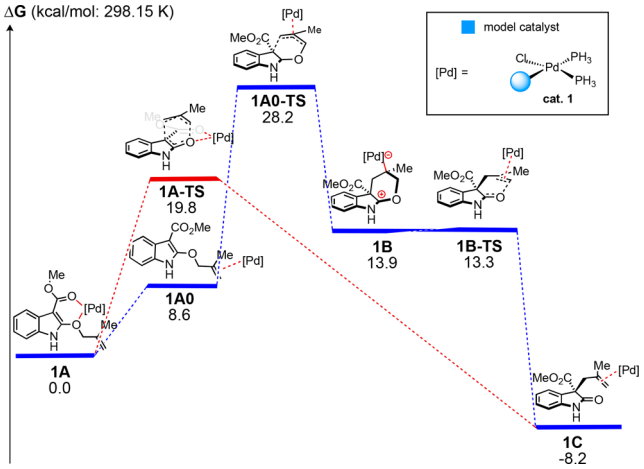

Figure 1. Competing reaction pathways for the Pd-catalyzed [3,3]-sigmatropic rearrangement of 2-allyloxyindoles.

shift (via **1A-TS**) leading to the product **1C**. The overall barrier is 19.8 kcal/mol, and the products lie 8.2 kcal/mol downhill. In contrast, the alternative Pd(II)-catalyzed pathway via π-coordination to the alkene (**1A0**) is much higher in energy (28.2 kcal/mol via **1A0-TS**) and stepwise, albeit via shallow intermediate **1B**. These results are in agreement with the experiment and show the importance, and role, of the 3-ester functionality in accelerating the reaction. That is, experimentally, the reaction proceeded at low temperatures (0 °C) and the substrate scope was limited to substrates bearing a carbonyl substituent at the C3-position.[9]

Next, we examined the energetics for the related Pd(II)-catalyzed [3,3]-sigmatropic shift of 3-ester-2-*propargyl*-oxyindoles. As shown in Figure 2, similar to the 3-ester-2-

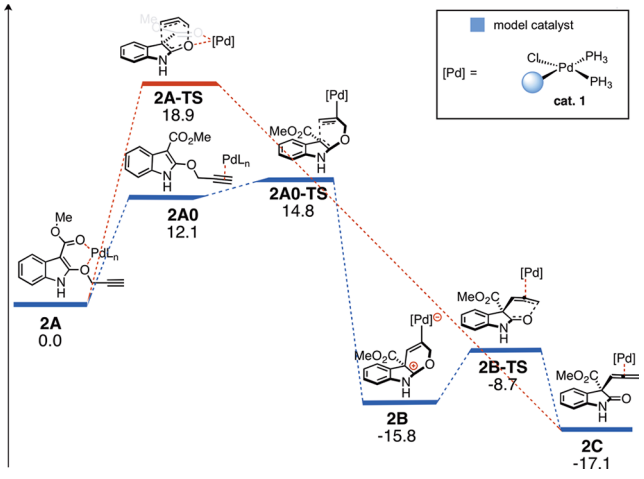

Figure 2. Competing reaction pathways for the Pd-catalyzed [3,3]-sigmatropic rearrangement of 2-propargyloxyindoles.

*allyl*oxyindoles, Lewis acid coordination to carbonyl and ethereal moieties (**2A**) is favored by ~12 kcal/mol over π-coordination (**2A0**). In addition, the Lewis acid promoted pathway proceeds in a concerted manner, while the π-activation pathway proceeds in a stepwise fashion. However, for the *propargyl* substrates, the barrier for the Lewis acid promoted rearrangement (via **2A-TS**) is much higher in energy (18.9 kcal/mol) than the π-activation, stepwise pathway (via **2A0-TS**). Overall, the lowest energy pathway proceeds via π-coordination (**2A0**) that activates the alkyne for nucleophilic attack by the indole (via **2A0-TS**) leading to low-lying intermediate **2B**. Finally, ring opening via **2B-TS** leads to the allenyl product (**2C**). Overall, the barrier for this process is 14.8 kcal/mol.

Intrigued by the apparent divergent mode of activation for these similar substrates, we next investigated the choice of computational method and counterion in the reaction barriers. As shown in Table 1, a screening of commonly used DFT

Table 1. Effect of DFT Method and Counterion on Relative Energetics between Competing Transtion States 1A-TS/1A0-TS and 2A-TS/2A0-TS

substrate	entry	computational method	counterion	$H_{LA} - H_{\pi}$ (kcal/mol)
1A	1	B3LYP/6-31G(d)-LANL2DZ-*gas*	Cl^-	4.9
	2	B3LYP/6-31G(d)-LANL2DZ*DCM*$_{(CPCM)}$	Cl^-	4.4
	3	B3LYP/6-31G(d)-SDD-*DCM*$_{(CPCM)}$	Cl^-	6.3
	4	B97*D*/6-31G(d)-SDD-*DCM*$_{(CPCM)}$	Cl^-	4.7
	5	M06L/6-31G(d)-SDD-*DCM*$_{(CPCM)}$	Cl^-	7.4
	6	B3LYP/LANL2DZ-*DCM*$_{(CPCM)}$	Cl^-	8.8
	7	B3LYP/LANL2DZ-*DCM*$_{(CPCM)}$	F^-	5.4
	8	B3LYP/LANL2DZ-*DCM*$_{(CPCM)}$	SbF_6^-	6.3
	9	B3LYP/LANL2DZ-*DCM*$_{(CPCM)}$	BF_4^-	6.7
2A	10	B3LYP/6-31G(d)-SDD-*DCM*$_{(CPCM)}$	Cl^-	−8.8
	11	M06L/6-31G(d)-SDD-*DCM*$_{(CPCM)}$	Cl^-	−5.3
	12	B3LYP/LANL2DZ-*DCM*$_{(CPCM)}$	Cl^-	−8.0
	13	B3LYP/LANL2DZ-*DCM*$_{(CPCM)}$	F^-	−7.8

functionals and counterions predicted the same divergent reactivity. That is, for alkenyl substrate **1A** the barrier for π-activation (via **1A0-TS**) is higher in energy by 4−9 kcal/mol than the Lewis acid pathway (via **1A-TS**). In contrast, for alkynyl **2A** substrate, the Lewis acid promoted rearrangement (via **2A-TS**) is higher in energy than the π-activation pathway (via **2A0-TS**) by 5−9 kcal/mol. A similar trend was observed using the full catalyst system $[PdCl(BINAP)]^+$ and a number of the substrates examined experimentally as outlined in the Supporting Information, SI). Overall, the relative energetics between the two pathways is unaffected by the method or by the use of truncated substrates/ligands.

To gain insight into the origin of the different reactivity, we applied a distortion−interaction analysis on the pathway determining transition state structures (e.g., **1A-TS**/**1A0-TS** and **2A-TS**/**2A0-TS**). Distortion−interaction analyses has been used to rationalize reactivities and selectivities of various organic and organometallic transformations.[15,16] As shown in Scheme 2, the energies [E_{total} (E_{tot}), $E_{distortion}$ (E_{dis}), and $E_{interaction}$ (E_{int})] for the Lewis acid activation (via **1A-TS** and **2A-TS**) are nearly identical for both substrates (Scheme 2, red). However, the energies for the π-activation are significantly different (Scheme 2, blue). For the *alkenyl*

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Scheme 2. Distortion–Interaction Model Analysis of Barriers[a]

alkenyl system	1A-TS	1A0-TS	propargyl system	2A-TS	2A0-TS
E_{tot}	24.1	29.0	E_{tot}	25.0	15.1
E_{dis}	42.1	58.2	E_{dis}	42.1	33.1
E_{int}	18.0	29.2	E_{int}	17.1	18.0

[a]Energies (kcal/mol) calculated using B3LYP/6-31G(d)-SDD(for Pd) in CH_2Cl_2 (CPCM) relative to complexed substrates **1A** and **2A** (see Figure 1 and Figure 2).

substrate **1A**, while both the magnitudes of distortion and interaction energies are greater in **1A0-TS**, the higher overall barrier for the π-activation pathway (e.g., **1A0-TS**) is attributed to a higher distortion energy (58.2 kcal/mol) versus only 42.1 kcal/mol for the concerted Lewis acid rearrangement (**1A-TS**). In contrast, for *alkynyl* substrate **2A**, the lower barrier of **2A0-TS** is attributed to a minor distortion in the transition state structure (33.1 kcal/mol) compared to **2A-TS** (42.1 kcal/mol). Note that the interaction energies for **2A-TS** and **2A0-TS** are nearly identical.

To gain insight into the origin of enantioselectivity, we modeled the diastereomeric transition states of 3-ester-2-propargyloxyindoles **2A** with the full chiral palladium(II) [Pd(*R*-BINAP)Cl]$^+$ (Figure 3). In agreement with experiment,

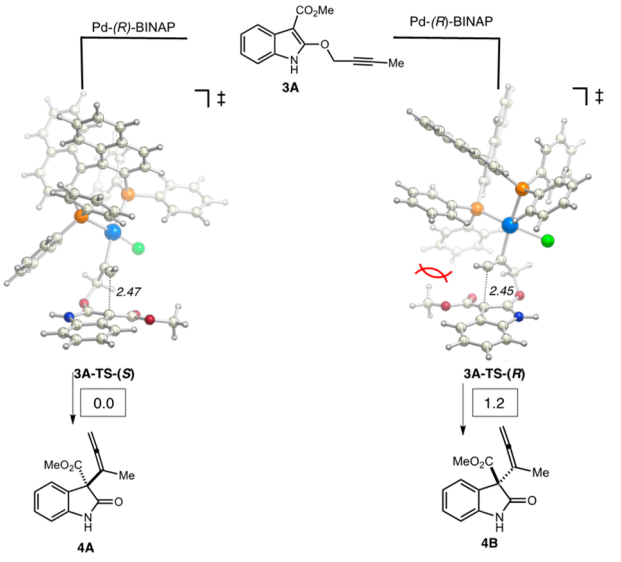
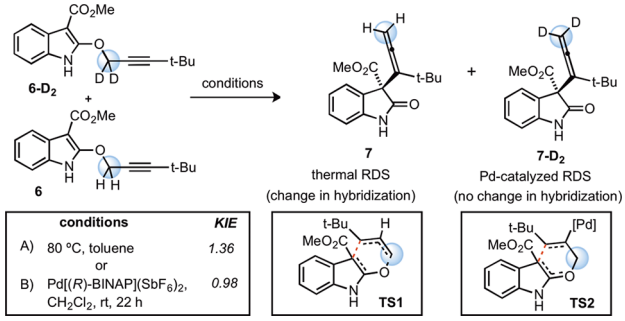


Figure 3. Origin of enantioselectivity in Pd(II)-(*R*)-BINAP-catalyzed [3,3]-sigmatropic rearrangement of 2-propargyloxyindoles. Relative energies are in kcal/mol, and distances in Å.

the lowest energy diastereomeric transition state places the ester group away from one of the phenyls of the chiral ligand leading to the major enantiomer **4A** (Figure 3, left).

Taken together, the different mode of reactivity is distortion-controlled wherein the alkynyl substrates proceed via π-activation (i.e., without coordination to the 3-ester moiety), and the enantioselectivity arises from lesser steric interactions between the ester and the ligand. As such, we hypothesize that the palladium(II)-catalyzed [3,3]-rearrangement of 2-propargylindoles can be expanded beyond the 3-ester-substituted substrates. To test these computational predictions experimentally, we probed the mechanistic picture presented in Figure 2 via deuterium labeling studies. We hypothesized that the concerted versus stepwise pathways would yield distinct secondary isotope effects.[17] Specifically, a concerted process, such as via **2A-TS** or the thermal rearrangement of a substrate deuterated at the propargylic position, would give rise to a normal, secondary isotope effect. On the other hand, no change in hybridization would occur at this center if reaction proceeds via **2A0-TS** and no isotope effect would be expected. Competition experiments with **6** and **6-D$_2$** under thermal conditions (Scheme 3) give rise to a secondary kinetic isotope

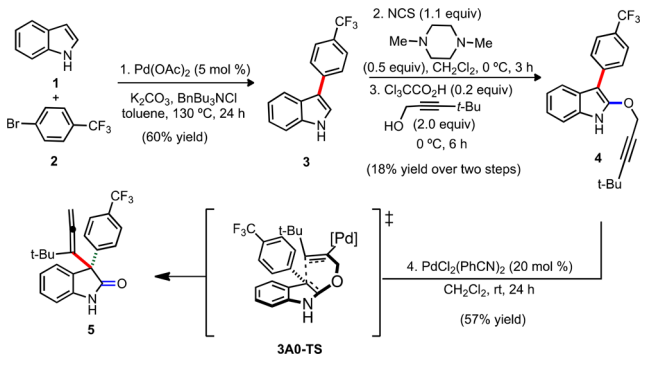
Scheme 3. Saucy–Marbet Claisen Rearrangement of 3-Aryl-2-propargylindoles



effect (k_H/k_D = 1.36 ± 0.05), which is consistent with the concerted reaction pathway (via **TS1**) predicted by calculations for the uncatalyzed reaction (see SI). On the other hand, we observed no secondary kinetic isotope effect under catalytic conditions (k_H/k_D = 0.98 ± 0.05). This result is consistent with the free-energy landscape depicted in Figure 2 where the rate-determining step (**2A0-TS**) does not involve changes of hybridization at the labeled methylene.

Previously, all substrates tested in this reaction possessed the 3-ester moiety. However, DFT calculations and kinetic isotope effect experiments support a stepwise mechanism via coordination to an alkyne (i.e., without the association of the ester to the metal in the rate-determining step). As a consequence, computations predict that 2-propargyloxyindoles without the 2-ester moiety should react under palladium catalysis. To probe this hypothesis, we designed a substrate **4** (Scheme 4) that would be electronically similar to substrate **6**. Thus, an electron-poor aryl ring was placed at the C3 position and the same bulky propargyl chain appended to the C2 position to slow any potential background [3,3]-sigmatropic reaction.[18] The coupling of indole **1** with aryl bromide **2** using

Scheme 4. Saucy–Marbet Claisen Rearrangement of 3-Aryl-2-propargylindoles



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conditions as reported by Bellina and Rossi,[19] followed by a two-step procedure to install the propargyloxy fragment, delivered **4** (Scheme 4). Notably, compound **4** was stable at room temperature for over a week without any detectable thermal [3,3]-sigmatropic rearrangement. As a proof-of-principle, we tested our computational predictions by subjecting **4** to 20% mol of $PdCl_2(PhCN)_2$ at room temperature. Under these conditions we found **4** delivered the rearrangement product **5** cleanly in 57% yield. These results provide experimental validation for the computations, which predicted a stepwise, low-temperature palladium-catalyzed rearrangement of propargyloxyindoles lacking the C3-ester functionality.

In conclusion, we have examined the mechanism of Pd(II)-catalyzed sigmatropic shifts of 3-allyloxy- and 3-propargyloxyindoles using density functional theory. These calculations revealed a divergent mode of reactivity which is surprising given that the same catalyst gives the same level of the enantioselectivity for the two similar substrates. Lower distortion energies control the reaction pathway, where a pathway involving Lewis acid coordination predominates for 3-allyloxyindole substrates and a pathway involving π-coordination predominates for 3-propargyloxyindoles. Labeling experiments are consistent with computational predictions. Further, for the first time, 3-propargyloxyindoles lacking the 3-ester functionality were found to be functional substrates for a palladium(II)-catalyzed rearrangement. This study represents a successful example using computational and experimental tools to elucidate the mechanism of a transformation and to broaden the substrate scope. Studies continue on the development of the asymmetric rearrangement of 3-aryl-2-propargyloxyindoles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02864.

Experimental procedures and spectroscopic data for all new compounds; structures of all minimized ground states and transition states (PDF)

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Notes

The authors declare no competing financial interest.

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(14) Unless otherwise specified, all calculations were carried out using Gaussian 09. For Figures 1 and 2, computed with M06L/6-31G(d)-SDD (for Pd) in CH_2Cl_2 (dielectric = 8.93) using the CPCM solvation model. For full model system (i.e., Figure 3), calculations were performed using B3LYP/LANL2DZ in CH_2Cl_2 (dielectric = 8.93) using the CPCM solvation model. Calculations using B3LYP/6-31G(d)-LANL2DZ-CH_2Cl_2(CPCM) yield similar results. See SI for additional computational details.

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