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Stereoselective Construction of α-Tetralone-Fused Spirooxindoles via Pd-Catalyzed Domino Carbene Migratory Insertion/Conjugate Addition Sequence

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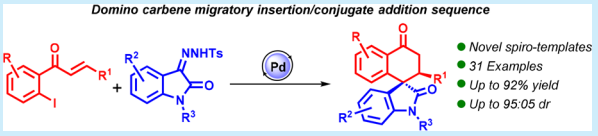
Supporting Information

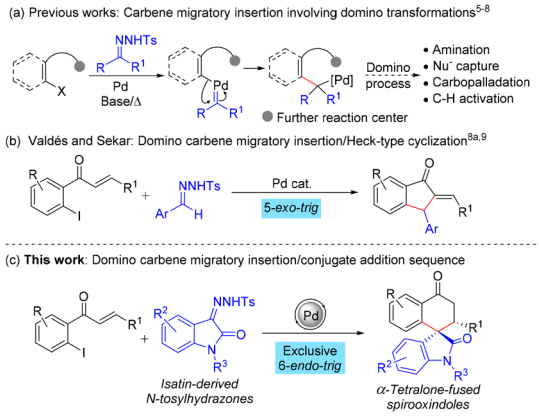
ABSTRACT: An efficient diastereoselective synthesis of α-tetralone-fused spirooxindoles is reported. The Pd-catalyzed domino reaction proceeds through a carbene migratory insertion followed by a 6-*endo-trig* mode of conjugate addition sequence from easily accessible isatin-derived *N*-tosylhydrazones and 2′-iodochalcones. The versatility of the protocol has been showcased by high functional group tolerance, broad substrate scope, and extension to an expedient synthesis of spiroacenaphthylenes. NMR reaction profiling and deuterium-labeling investigations provide insight into the mechanistic pathway.



The development of a novel catalytic domino reaction, which operates efficiently with high levels of stereoselectivity, is a paramount challenge in contemporary synthetic chemistry.[1] In this scenario, domino C−C bond formations involving metal carbene migratory insertion as a key step have been identified as a versatile strategy to construct complex cyclic architectures in a single operation (vide infra).[2] The intriguing reactivity of palladium makes it a potent catalyst in this field where the reaction is considered to proceed via Pd−carbenoid complex formation and subsequent migration of carbene into the Pd−C bond.[3] Though diazo compounds are widely utilized as a carbene precursors, the past decade has witnessed *N*-tosylhydrazones as safe and alternative nucleophilic coupling partners via in situ generation of diazo species.[4]

The Pd-catalyzed carbene migratory insertion process has been successfully merged with other transformations such as amination,[5] C- or O-nucleophilic capture,[6] C(sp^2)−H bond activation,[7] and carbopalladation[8] in an intramolecular fashion to build various cyclic molecular motifs (Scheme 1a). Along these lines, recently our group and Valdés et al. have independently reported the carbene migratory insertion/Heck-type cyclization sequence wherein the η^3-benzyl-Pd intermediate underwent 5-*exo-trig* mode of carbopalladation followed by the β-H elimination to afford 2-arylidine-1-indanones with *E*-selectivity (Scheme 1b).[8a,9] We anticipated that the cyclic tosylhydrazones might behave in a similar way to synthesize structurally complex spirocycles, remarkably with a tetrasubstituted carbon center. The choice of cyclic tosylhydrazones would be the crucial factor in the aforementioned concept as the transient alkyl/benzyl σ-Pd intermediate prone to undergo β-H elimination to deliver Barluenga coupling product rather than engaging in further transformations.[10] In this context, the significant deviation in the behavior of π-oxoallyl palladium intermediate has been uncovered when rigid isatin-derived *N*-tosylhydrazones were employed. Herein, we report the highly diastereoselective synthesis of α-tetralone-fused spirooxindoles through a novel domino carbene migratory insertion followed by 6-*endo-trig* mode of conjugate addition sequence under mild reaction conditions (Scheme 1c).

Scheme 1. Pd-Catalyzed Carbene Migratory Insertion in the Construction of Cyclic Motifs



It should be mentioned that spirooxindoles are important motifs found in many natural and pharmaceutically active molecules.[11] Among them, 6-membered carbocyclic-fused spirooxindoles own a unique molecular architecture.[12,13] The development of methods to build such scaffolds has received less attention in the synthetic community which include pericyclic approach,[13a] Michael−aldol domino reaction,[13b] and spirocyclization via C−H bond activation/benzyne insertion sequences.[13c] However, most of these studies are limited to low convergence and moderate diastereoselectivities.

We commenced our investigation by using 2′-iodochalcone **1a** and *N*-Me-protected isatin-derived tosylhydrazone **2** in the presence of 10 mol % of $Pd(OAc)_2$, 30 mol % of PPh_3, and 3.0

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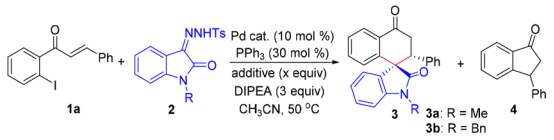
equiv of DIPEA as a base in CH_3CN at 80 °C. To our delight, **3a** was formed in 36% yield with 72:28 dr (*anti*/*syn*),[14] along with a significant amount of 3-phenyl-1-indanone **4** as side product, presumably arising from a reductive Heck cyclization of **1a** which has been reported under similar reaction conditions (Table 1, entry 1).[15] It should be noted that product **5** (for structure, see Scheme 6) arising via a 5-*exo*-*trig* mode of oxidative Heck-type cyclization was not detected in ^{1}H NMR of the crude reaction mixture. Study of a suitable *N*-protecting group of **2** showed that the efficacy could be improved with *N*-Bn as it provided **3b** in increased yield and modest dr of 73:27 (entry 3). The structures and relative configuration of both diastereomers were unequivocally determined by NMR and XRD analyses.[14] Decreasing the reaction temperature to 50 °C subsided the side product formation efficiently, and thus, further screenings were carried out at 50 °C. Of the catalysts tested, the $[Pd(\eta^3\text{-allyl})Cl]_2$ complex was found to be the best choice in terms of both yield and stereocontrol (entry 8). Further investigation of the ligands, bases, and solvents did not improve the yield or the dr of the reaction.

The addition of 1.0 equiv of HCOONa or proton sponge as external reducing agents that has been reported to be operative in other reductive Heck reactions did not improve the yield and diastereoselectivity (entries 9 and 10), while the addition of 1.0 equiv of H_2O led to yield of 63% (entry 11). Previously, Cacchi et al. reported that combination of quaternary ammonium salts and tertiary amines could enhance the formation of conjugate addition type product by stabilizing the alkyl σ-Pd intermediates.[16] As anticipated, an inclusion of 50 mol % of TBAC improved the yield to 76% with 89:11 dr (entry 12). Further screening of various quaternary ammonium salts and loading revealed that using of 25 mol % of TBAB was efficient as it furnished **3b** in 86% of isolated yield with 91:09 dr (entry 14). We noted that employing rigorously dried solvent and reagents led to the decrease in the yield (31%), indicating that presence of trace amount of moisture in the reaction might be responsible for protonolysis (entry 16). A one-pot reaction through in situ generation of tosylhydrazone provided **3b** in 54% yield with 89:11 dr (entry 17).[14]

Armed with optimized conditions, the scope for the synthesis of spirocycles was then broadened (Scheme 2). Electron-donating (−Me, −^{t}Bu, and −OMe) or electron-withdrawing (−F, −CF_3, −CO_2Me, and −CN) substituents present at the 4-position of the aryl ring in 2′-iodochalcones underwent the transformation smoothly, providing the corresponding products in good to excellent yields and dr (**3b**–**j**). Moreover, strong electron-withdrawing groups such as −F and −NO_2 were also well tolerated to deliver the desired products **3m** and **3o** with comparable yields and dr. It is noteworthy that the sterically hindered *o*-methyl group afforded **3p** in relatively higher dr (95:05) than other substrates albeit with a moderate yield of 70%. When the phenyl ring was replaced with β-naphthyl or heterocycles such as 2-furyl and 2-thienyl systems, the domino process afforded products (**3r**–**t**) with good yield and selectivity,

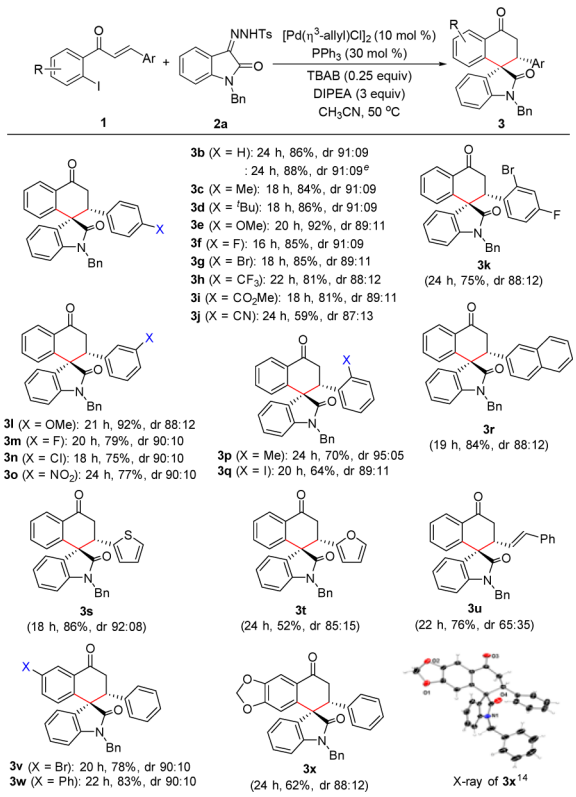
Table 1. Optimization of the Reaction Conditions[a]



entry	R	Pd cat.	additive (equiv)	yield (%) 3/4[b,c]	dr[b] *anti*/*syn*
1[d]	Me	$Pd(OAc)_2$		36/24	72:28
2[d]	Ts	$Pd(OAc)_2$		15/36	67:33
3[d]	Bn	$Pd(OAc)_2$		56/28	73:27
4	Bn	$Pd(OAc)_2$		46/5	86:14
5[e]	Bn	$Pd(PhCN)_2Cl_2$		48/8	73:27
6[e]	Bn	$Pd_2(dba)_3$		56/7	77:23
7	Bn	[Pd(cinnamyl) Cl]$_2$		62/0	82:18
8	Bn	$[Pd(\eta^3\text{-allyl})Cl]_2$		69/0	88:12
9	Bn	$[Pd(\eta^3\text{-allyl})Cl]_2$	HCOONa (1)	68/0	84:16
10	Bn	$[Pd(\eta^3\text{allyl})Cl]_2$	Proton Sponge (1)	61/7	87:13
11	Bn	$[Pd(\eta^3\text{-allyl})Cl]_2$	H_2O (1)	63/5	85:15
12	Bn	$[Pd(\eta^3\text{-allyl})Cl]_2$	TBAC (0.5)	76/0	89:11
13	Bn	$[Pd(\eta^3\text{-allyl})Cl]_2$	TBAB (0.5)	80/0	90:10
14[f]	Bn	$[Pd(\eta^3\text{-allyl})Cl]_2$	TBAB (0.25)	89 (86)/0	91:09
15	Bn	$[Pd(\eta^3\text{-allyl})Cl]_2$	TBAB (0.1)	72/0	89:11
16[g]	Bn	$[Pd(\eta^3\text{-allyl})Cl]_2$	TBAB (0.25)	31/0	86:14
17[h]	Bn	$[Pd(\eta^3\text{-allyl})Cl]_2$	TBAB (0.25)	54/0	89:11

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), Pd catalyst (10 mol %), CH_3CN (1 mL) at 50 °C for 16–24 h. [b]Determined by ^{1}H NMR of the crude using 1,3,5-trimethoxybenzene as an internal standard. [c]Yield of both the diastereomers. [d]Reaction at 80 °C. [e]Unreacted **1a** was found (18% for entry 5 and 11% for entry 6). [f]Values in parentheses represent isolated yields. [g]Reaction in dry CH_3CN and N_2 atmosphere. [h]One-pot reaction starting from *N*-Bn-isatin.

Scheme 2. Substrate Scope with 2′-Iodochalcones[a–d]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol) in CH_3CN (3 mL) at 50 °C. [b]Isolated yields. [c]dr's were determined by ^{1}H NMR of the crude reaction mixture. [d]Indicated major diastereomers were assigned by analogy based on the X-ray structure of **3a**, **3b**, and **3x**. [e]Reaction is on 3.0 mmol scale.

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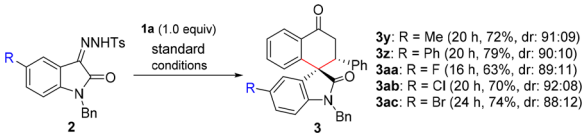
while the *trans*-cinnamyl-substituted chalcone **1u** was converted into the corresponding product **3u** in 76% yield with diminished dr of 65:35, presumably due to less steric demand of styryl group than the aryl group. This finding also suggests that diastereoselectivity might be governed by the substituent present at the carbonyl β-position.

Subsequently, the effect of substituents of the isatin-derived tosylhydrazones **2** was investigated (Scheme 3). Electron-rich

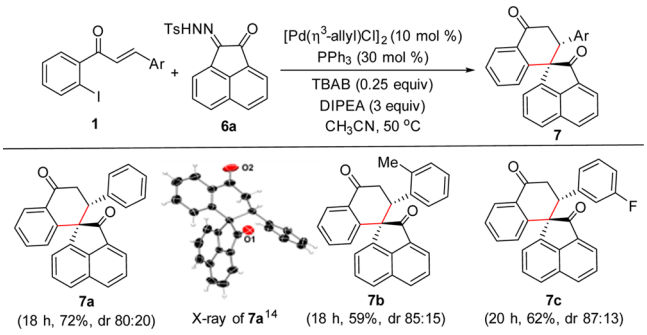
Scheme 3. Scope of the Isatin-Derived *N*-Tosylhydrazones



hydrazones were efficiently annulated to afford desired products in 72% and 79% yields with 91:09 and 90:10 dr, respectively (**3y** and **3z**). Halo-substituted tosylhydrazones were also identified as viable substrates to deliver the products (**3aa**–**ac**) in 63–74% yields and 88:12–92:08 dr.

Furthermore, we investigated the applicability of our methodology toward the synthesis of spiroacenaphthylenes by utilizing acenaphthenequinone-derived tosylhydrazones. Optimized reaction conditions do indeed allow access to spirocycles **7** in good yields and with slightly diminished stereocontrol (Scheme 4).

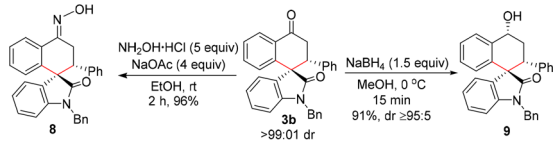
Scheme 4. Domino Synthesis of Spiroacenaphthylenes



Again, no reductive Heck **4** or 5-*exo-trig* cyclization products were detected. The structure of major isomer **7a** was determined to be the *anti*-isomer, and those of **7b** and **7c** were assigned by analogy.

Next, the follow-up reactions were carried out to investigate the utility of spirooxindoles (Scheme 5). Compound **3b** was readily

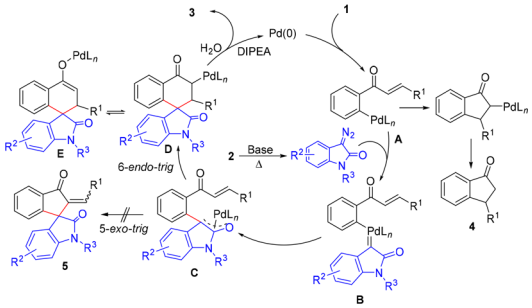
Scheme 5. Diversification of Spirooxindoles



functionalized upon condensation with hydroxylamine to give *E*-oxime **8** in almost quantitative yield. Reduction of the carbonyl group by $NaBH_4$ led to an excellent diastereoselective formation of alcohol **9** in 91% yield.

Based on our experimental observations and literature precedent,[9,17] a plausible mechanism is outlined in Scheme 6. Initially, oxidative addition of **1** to Pd(0) generates ArPd(II) species **A** which would react with in situ formed diazo compound

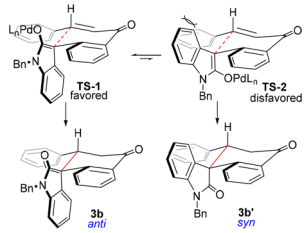
Scheme 6. Proposed Reaction Pathway



to give the Pd–carbenoid complex **B**. Then, the intermediate **B** may evolve through the migratory insertion of the aryl group into carbenic carbon atom to generate the C- or O-bound Pd-enolate which would exist as π-oxoallyl Pd-intermediate **C**. Then, the Pd-enolate undergoes an intramolecular 6-*endo-trig* mode of conjugate addition to form intermediate **D**. Since *syn*-β-H elimination precluded by the conformationally rigid nature, intermediate **D** or its corresponding O-bound tautomer **E** undergoes protonolysis to furnish the product. The resultant Pd(II) reduced to active Pd(0) with the aid of DIPEA. The formation of **5** via a 5-*exo-trig* mode of closure is disfavored presumably due to increased steric hindrance involved in the approach of the Pd to α-position of the double bond.

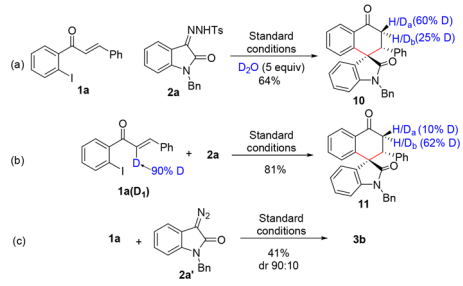
The conjugate addition may proceed through a six-membered chairlike transition state **TS-1** wherein the less sterically demanding amide part of the isatin is equatorially disposed, leading to *anti*-isomer **3b** as a major product. The unfavorable steric interaction caused by the benzene core of isatin with aryl ring of **1a** in **TS-2** results in the minor isomer **3b′** (Scheme 7).

Scheme 7. Rationalization of Diastereoselectivity



To understand the mechanism, a deuterium-labeling experiment was performed in the presence of 5 equiv of D_2O furnished **10** with extensive D-incorporation (85%) at the carbonyl α-position, as determined by ^1H NMR (Scheme 8a). It clearly illustrates that the moisture present in the reaction medium is the main source of the proton rather than the hydride from Hünig's

Scheme 8. Control Experiments



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base. Unequal D-distribution between the diastereotopic hydrogens could be reasoned that steric hindrance rendered by the aryl ring present at the β-position. Later, the synthesized α-deuterated 2′-iodochalcone afforded **11** with 10% and 62% of D_a and D_b atoms, respectively, which supports the tautomerization involved in the prefinal step of our proposed mechanism (Scheme 8b). The loss of D-content could be explained by the H/D exchange between **11** and moisture present in the reaction media.[18] While the preformed diazo compound **2a′** was subjected, **3** was formed in 41% yield which proves that reaction proceeds via diazo intermediate (Scheme 8c). It also implies that the use of *N*-tosylhydrazones as carbene precursors led to better yields than the direct usage of unhandy diazo compounds, highlighting the versatility of the protocol.

Additionally, a time-dependent reaction profiling by NMR was done to study the reaction kinetics (Figure 1). ^{1}H NMR yields

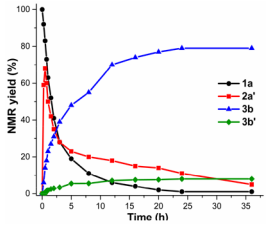

Figure 1. Reaction profile of the domino process.

over time revealed that 70% of diazo intermediate **2a′** was observed within 30−45 min, which then consumed gradually during the course of the reaction. Moreover, the dr between the products **3b** and **3b′** was remained constant (90:10) throughout the reaction which suggests that diastereoselectivity was defined by the thermodynamic control. However, a detailed mechanistic study and efforts to make asymmetric variants are currently underway in our laboratory.

In conclusion, we have developed a novel Pd-catalyzed carbene migratory insertion/conjugate addition strategy to access spirooxindoles with contiguous quaternary and tertiary carbon centers in a diastereoselective fashion. This operationally simple protocol represents the first example of isatin-derived *N*-tosylhydrazones being utilized in a metal-carbenoid involving domino process and opens up a new way to construct novel complex molecular spirocycles from readily accessible starting materials with a broad scope. A transition-state model has been proposed to understand the observed stereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02555.

Experimental procedures, characterization data for all products, NMR spectra, and single-crystal XRD data (PDF)

X-ray data for compounds **3a**, **3a′**, **3b**, **3b′**, **3x** and **7a** (CIF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. S. Sankararaman on his 60th birthday.

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(18) 51% of D-atom at the methylene position (37% of D_a and 14% of D_b) was observed when treating **3b** with 5 equiv of D_2O under standard conditions.

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