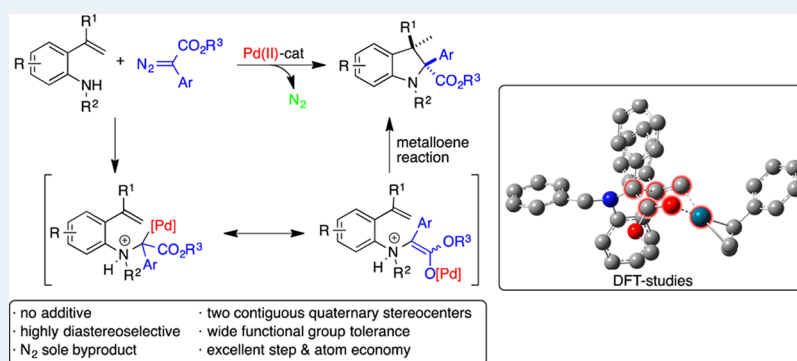


Stereoselective Palladium-Catalyzed Synthesis of Indolines via Intramolecular Trapping of *N*-Ylides with AlkenesAngula Chandra Shekar Reddy,<sup>†</sup> Venkata Surya Kumar Choutipalli,<sup>‡</sup> Jayanta Ghorai,<sup>†</sup> Venkatesan Subramanian,<sup>‡</sup> and Pazhamalai Anbarasan<sup>\*,†</sup><sup>†</sup>Department of Chemistry, Indian Institute of Technology Madras, Chennai 600036, India<sup>‡</sup>Chemical Laboratory, CSIR-Central Leather Research Institute, Chennai 600020, India

## Supporting Information



**ABSTRACT:** Metal-catalyzed in situ functionalization of ammonium ylides has emerged as a mild and atom/step economy strategy for the construction of complex building blocks. Despite the success, these trapping reactions are limited to activated polar double bonds such as ( $\alpha,\beta$ -unsaturated) carbonyl derivatives. Trapping of ammonium ylides with nonpolar double bonds, which allows the all-carbon quaternary center, is unprecedented. In this article, an efficient stereoselective palladium-catalyzed intramolecular trapping of *N*-ylides derived from *o*-vinylaniline and  $\alpha$ -diazocarbonyl compounds has been accomplished, a carbenylative hydroamination of alkenes. The present reaction allows the synthesis of various tri- and tetrasubstituted indolines in good yield with high diastereoselectivity. Important features are the construction of two contiguous quaternary carbon centers via the formation of C–N and C–C bonds in a single operation, high diastereoselectivity, wide functional group tolerance, and high atom and step economy. A reaction mechanism has also been explored by a combination of experimental and DFT studies, which revealed the formation of *N*-ylide followed by cyclization through metallo–ene-type reaction involving a six-membered cyclic transition state, where the diastereoselectivity is also established.

**KEYWORDS:** carbenylative hydroamination, ylide, palladium, indoline, metalloene reaction, alkene, DFT

## INTRODUCTION

Donor–acceptor metal carbenoids derived from  $\alpha$ -diazocarbonyl compounds have emerged as highly reactive and valuable intermediates in organic chemistry.<sup>1</sup> These metal carbenoids, derived from dirhodium and copper complexes, were demonstrated to possess highly electrophilic character<sup>2</sup> that undergoes numerous transformations<sup>3</sup> such as cyclopropanation,<sup>4</sup> insertion into C/heteroatom–H bond,<sup>5</sup> and functionalization via generation of ylide.<sup>6</sup> Besides, cross-coupling reactions of palladium carbenoids were also reported.<sup>7</sup> Among these reactions, multicomponent reactions<sup>8</sup> of diazo-carbonyl compounds and amines/alcohols with reactive electrophiles, via generation and trapping of N/O-ylides, have gained significant attention in recent years due to the high atom and step economy and possible construction of complex molecules with high diversity and selectivity (Scheme 1a, right side).<sup>9</sup> To date, reactive electrophiles that were utilized are polar double bonds such as aldehydes/ketones,<sup>10</sup> imines,<sup>11</sup> and

$\alpha,\beta$ -unsaturated carbonyl/nitro compounds.<sup>12</sup> However, trapping of ylides with nonpolar double bonds, i.e., simple alkene, is not documented and highly challenging for the following reasons: (1) low reactivity of nonpolar double bonds toward the trapping of ylides and (2) fast 1,2-proton transfer in ylides would result in the formation of inserted product (Scheme 1a).

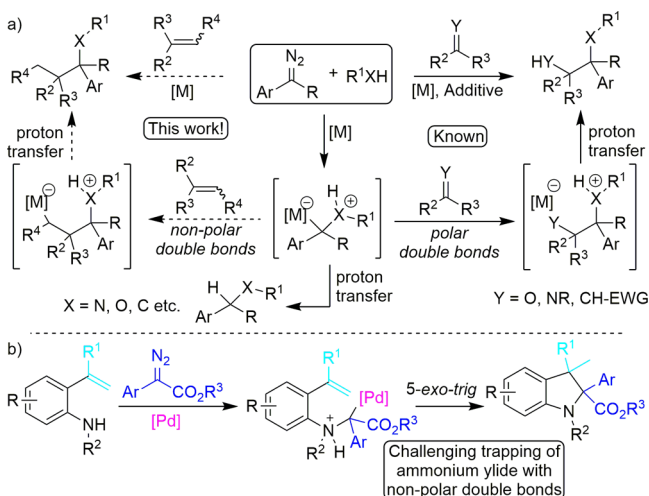
To increase the reactivity of simple alkene and to suppress the 1,2-proton transfer, we envisioned an intramolecular reaction with *o*-vinylaniline and diazo compound employing suitable palladium catalyst (Scheme 1b), well established to insert an alkene into Pd–C/heteroatom bond under Heck-type reaction.<sup>13</sup> Successful demonstration of this trapping would provide novel transformation, viz. carbenylative hydroamination of alkene,<sup>14</sup> and would also allow the synthesis of

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**Scheme 1. (a) Transition-Metal-Catalyzed Functionalization of Ylide; (b) Proposed Pd-Catalyzed Carbenylative Hydroamination of Alkenes**



polysubstituted indolines,<sup>15</sup> which are ubiquitous subunits present in various biologically relevant molecules.<sup>16</sup> On the basis of these challenges, its importance, and as part of our ongoing interest in exploring the new reactivity of metal carbenoids,<sup>17</sup> we herein disclose the first diastereoselective palladium-catalyzed intramolecular carbenylative hydroamination of *o*-vinylaniline for the construction of tri- and tetrasubstituted indolines and its mechanistic insight.

## RESULTS AND DISCUSSION

On the basis of the hypothesis, *o*-vinylanilines **1a–e** having electronically different substitution at nitrogen were synthesized and subjected under the palladium-catalyzed carbenylative hydroamination conditions with diazo compound **2a**. After the initial screening of various catalyst and critical parameters, [Pd(cinnamyl)Cl]<sub>2</sub> was chosen as a suitable catalyst in toluene at 100 °C (see Supporting Information). Electron-rich aniline **1a** on reaction with **2a** did not afford either the expected product **3a** or the inserted product **4a**, instead leading to the

rapid decomposition of diazo compound **2a** (Table 1). Similar result was observed with related electron-donating (*p*-methyl)-benzyl and electron-withdrawing, carbamate, amide, and sulfonamide-containing *o*-vinylanilines **1b** and **1c**, **1d**, and **1e**, respectively. To our delight, slow addition of **2a** to the mixture of **1b** and [Pd(cinnamyl)Cl]<sub>2</sub> in toluene at 100 °C gave the expected product **3b** in 50% isolated yield as single diastereoisomer; another diastereoisomer was not detected in both <sup>1</sup>H NMR and HPLC analysis, and no inserted product **4b** was observed. On the other hand, slow addition of **2a** with other anilines **1a** and **1c–e** under the above conditions also did not afford any expected products.

Next, to improve the yield of **3b**, the influence of ligands was examined with various electronically and sterically different phosphines, such as PPh<sub>3</sub>, (2-furyl)<sub>3</sub>P, (*o*-tolyl)<sub>3</sub>P, X-Phos, etc. All ligands furnished **3b** in ~48% yield, suggesting that ligands do not show any significant influence on the present reaction; hence, a ligand-free palladium system was chosen for further optimization. Similarly, introduction of additive like base and copper salts also did not improve the reaction (see Supporting Information). Successfully, increasing the reaction temperature to 120 °C and catalyst loading to 6 mol % gave the product **3b** in 84% yield.

Having successfully optimized the palladium-catalyzed carbenylative hydroamination, the scope and limitation of diazo compounds and *o*-vinylanilines were investigated. First, diverse substitutions on the aryl moiety of aniline **1** were examined (Scheme 2). Simple phenyl- and alkyl-substituted aniline derivatives afforded **3f–i** in good yield. Reactive functional groups such as benzyloxy (**3j**), acetoxy (**3n**), tosyloxy (**3o**), TBDMS ether (**3k**), acetal (**3l**), carboxylic ester (**3p**), fluoro (**3m**), and vinyl (**3r**) were well tolerated under the optimized conditions. The structure and diastereoselectivity, *cis* relation of both phenyl groups, was unambiguously confirmed by single-crystal X-ray analysis of **3m**.<sup>18</sup> Introduction of steric hindrance ortho to the vinyl group was well accepted and led to the formation of **3q** in 77% yield; on the other hand, substitution ortho to the nitrogen did not afford the indoline **3t**. Subsequently, varying the nucleophilicity of amine by substituting with an electronically different benzyl

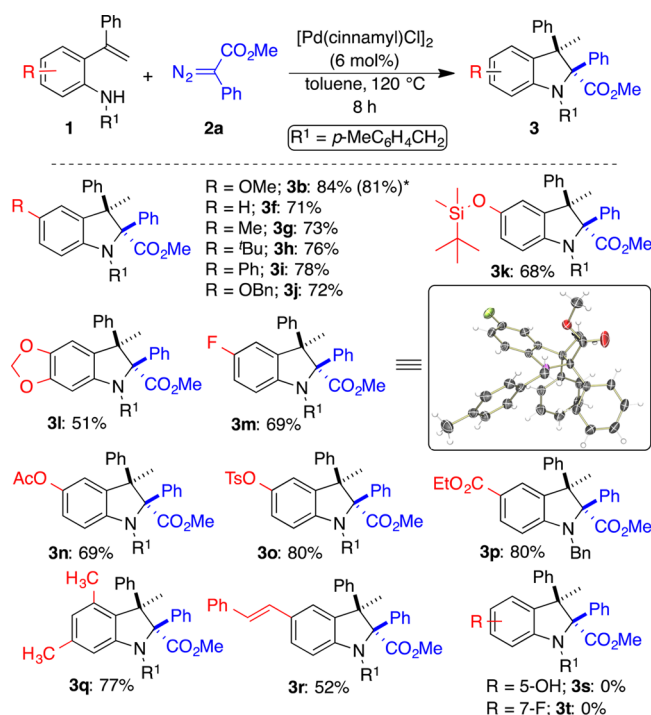
**Table 1. Palladium-Catalyzed Carbenylative Hydroamination of *o*-Vinylaniline **1** and Diazo Compound **2a**: Optimization<sup>a</sup>**

entry	R	X, mol %	ligand	yield of <b>3</b> (%) <sup>b</sup>
1	H ( <b>1a</b> )	3		0
2	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> ( <b>1b</b> )	3		0 (50) <sup>c</sup>
3	COOEt ( <b>1c</b> )	3		0
4	COCF <sub>3</sub> ( <b>1d</b> )	3		0
5	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> ( <b>1e</b> )	3		0
6	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> ( <b>1b</b> )	3	PPh <sub>3</sub>	47 <sup>c</sup>
7	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> ( <b>1b</b> )	3	(2-furyl) <sub>3</sub> P	45 <sup>c</sup>
8	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> ( <b>1b</b> )	3	( <i>o</i> -tolyl) <sub>3</sub> P	48 <sup>c</sup>
9	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> ( <b>1b</b> )	3	X-Phos	48 <sup>c</sup>
10	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> ( <b>1b</b> )	6		66 <sup>c</sup> (84) <sup>d</sup>

<sup>a</sup>Reaction conditions: **1a** (1 equiv), **2a** (2 equiv), [Pd(cinnamyl)Cl]<sub>2</sub> (X mol %), lgand (10 mol %), toluene, 100 °C, 8 h. <sup>b</sup>All are isolated yield.

<sup>c</sup>Slow addition of **2a**. <sup>d</sup>At 120 °C.

**Scheme 2. Palladium-Catalyzed Carbenylative Hydroamination: Scope of Anilines<sup>a</sup>**



<sup>a</sup>Reaction conditions: **1** (1 equiv), **2a** (2 equiv), [Pd(cinnamyl)Cl]<sub>2</sub> (6 mol %), toluene, 120 °C, 8 h. All compounds are isolated as a single diastereomer. \*Yield of gram scale (1 g of **1b**) reaction.

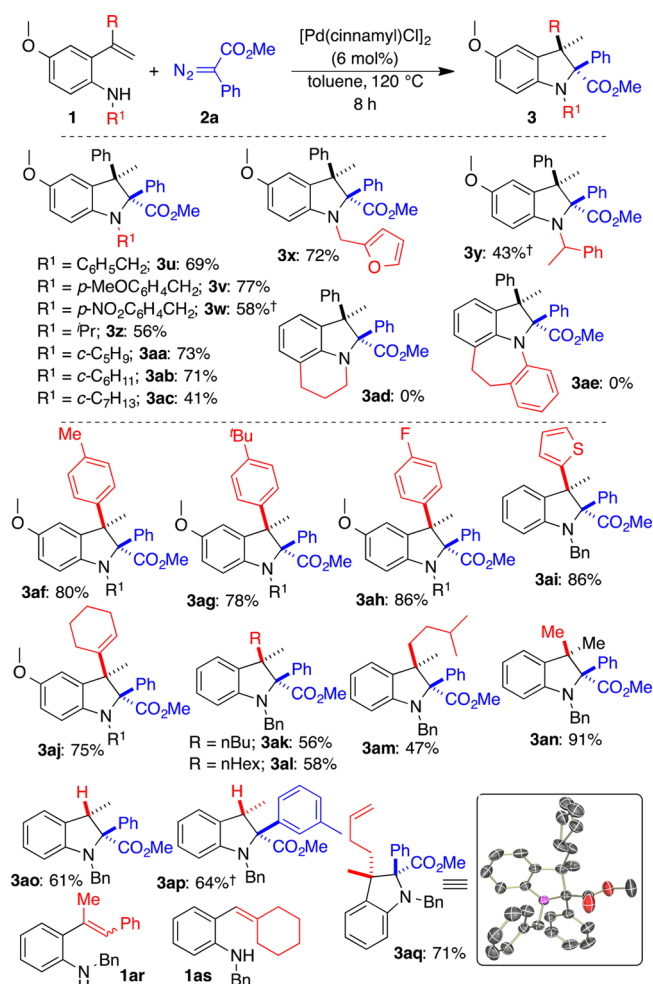
moiety was well tolerated to give the products **3u–x** in good yield (Scheme 3). Introduction of a methyl group at the benzylic position and replacing benzyl with an alkyl moiety, like isopropyl and cycloalkyl, also furnished corresponding indolines. However, amine being part of the fused ring did not afford the cyclized product, possibly due to the ring strain during cyclization. It is important to note that gram-scale reaction of **1b** and **2a** afforded the indoline **3b** with no loss in the yield (81%, Scheme 2), which was very important with respect to synthetic applicability and scalability.

Next, changing the phenyl group on the alkene moiety with *p*-tolyl, *p*-*tert*-butylphenyl, *p*-fluorophenyl, and thiophen-2-yl afforded the indolines **3af–ai** in ~80% yield (Scheme 3). Interestingly, alkenyl and alkyl substituents on alkenes were well tolerated to furnish **3aj–an** in comparable yield. Unsubstituted alkene was also successfully converted to corresponding 2,2,3-trisubstituted indoline **3ao** and **3ap** in good yield. Similar to  $\alpha$ -substituted styrenes,  $\alpha,\beta$ -disubstituted styrene also underwent efficient reaction to furnish **3aq** in 71% yield, and it was unambiguously confirmed by X-ray analysis.<sup>19</sup> Unfortunately, *o*-alkenylaniline **1ar** and **1as**, which has a bulky group at the  $\beta$ -position and  $\beta,\beta$ -disubstitution, respectively, did not give the expected cyclized products.

Next, the scope and limitation of diazo compounds was examined. Similar to methyl ester, ethyl ester gave the product **3at** in 83% yield (Scheme 4). However, bulky isopropyl and *tert*-butyl esters and additional coordination containing allyl ester failed to furnish expected indolines **3au–aw**; instead, N–H inserted products **4au**, **4av**, and **4aw** were observed in 72%, 62%, and 68% yield, respectively.

Electronically different aryl groups on **2** were well tolerated under the present conditions to afford **3ax–bf** in good yield.

**Scheme 3. Palladium-Catalyzed Carbenylative Hydroamination: Scope of Anilines<sup>a</sup>**



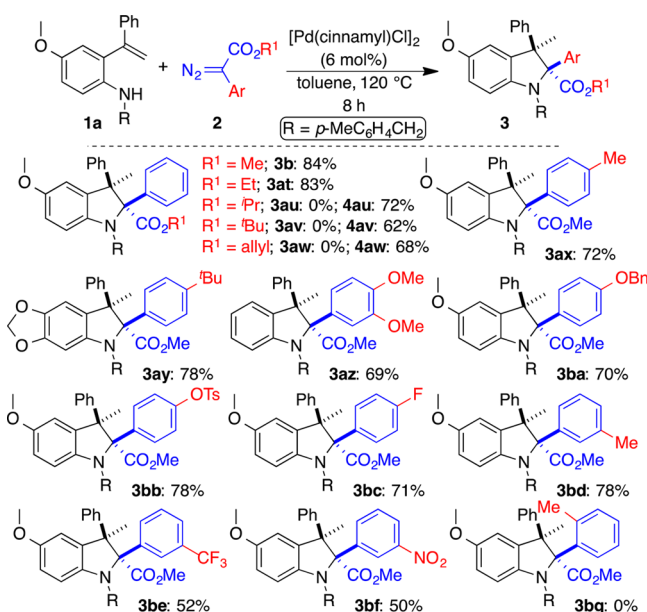
<sup>a</sup>Reaction conditions: **1** (1 equiv), **2a** (2 equiv), [Pd(cinnamyl)Cl]<sub>2</sub> (6 mol %), toluene, 120 °C, 8 h. All compounds are isolated as single diastereomer. <sup>†</sup><sup>1</sup>H NMR Yield

Interestingly, pharmaceutically important trifluoromethyl-substituted indoline **3be** was also achieved from the corresponding diazo compound **2**. Similar to the previous observation, sterically demanding ortho-substituted aryl-containing diazo compounds did not afford the cyclized product.

To understand the mechanism of reaction, **1b** and **2a** were treated under standard conditions in the presence of excess of D<sub>2</sub>O. The reaction afforded a mixture of **3b** and deuterated indoline **3b'** in a 1:0.3 ratio (Scheme 5). Analysis of the reaction mixture after 1 h gave 52% of a mixture of **3b** and **3b'** along with 40% of **1b**. Although the ratio of **3b** and **3b'** remained comparable, no deuterium incorporation was observed in the recovered **1b**.

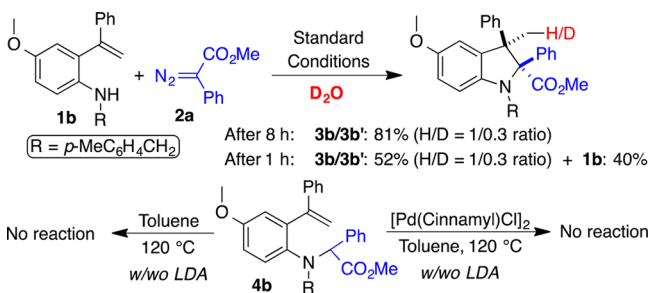
These results suggest the formation of **3b'** is not due to the Pd-catalyzed C–H bond activation; instead, the catalytic palladium ends up at the methylene carbon after cyclization. Next, to assess the feasibility of **4b** being the intermediate in the present transformation, various attempts were made to cyclize to corresponding indoline. All attempts have failed, suggesting that **4b** may not be an intermediate and could be formed from N-ylide when the trapping is slow or with unfavorable conditions. Next, a number of NMR experiments were

**Scheme 4. Palladium-Catalyzed Carbenylative Hydroamination: Scope of Diazo Compounds<sup>a</sup>**



<sup>a</sup>Reaction conditions: **1a** (1 equiv), **2** (2 equiv), [Pd(cinnamyl)Cl]<sub>2</sub> (6 mol %), toluene, 120 °C, 8 h. All compounds are isolated as single diastereomer.

**Scheme 5. Control Experiments**

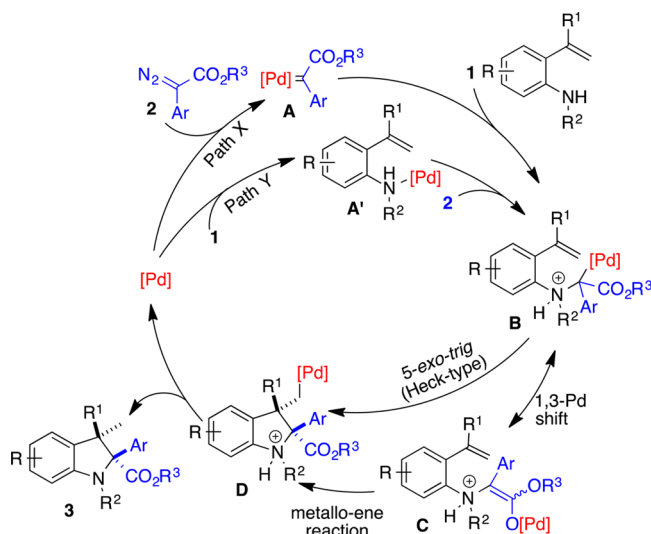


performed at variable temperatures to identify the potential intermediate and reaction mechanism, which also failed to provide any conclusive information. It remained as a question about the possible intermediate and the observed diastereoselectivity, which sought the help of DFT studies.

On the basis of the preliminary mechanistic investigation and to gain the mechanistic details, we postulated the following mechanism and evaluated it by theoretical studies at the DFT level. As shown in **Scheme 6**, initial formation of *N*-ylide **B** from **1**, **2**, and Pd-catalyst could be achieved through either carbenoid **A** or amine complex **A'** (Paths X and Y). Similarly, formation of cyclized **D** from **B** can also be rationalized in two pathways: (1) the Pd–C bond in **B** could undergo intramolecular Heck-type reaction under a *5-exo-trig* mode of cyclization and (2) metallo–ene reaction of palladium species **C**, generated from **B** via the 1,3-Pd shift. Final protonation of **D** would furnish the observed indoline **3** along with regeneration of palladium catalyst to continue the catalytic cycle.

This postulated mechanism has been comprehensively investigated employing DFT calculations, and the energy profiles and all optimized geometries are depicted in **Figure 1** and **Figures S1–3** (see **Supporting Information**). The reaction starts with initial formation of *N*-ylide **B** and occurs via pathway

**Scheme 6. Plausible Mechanism**



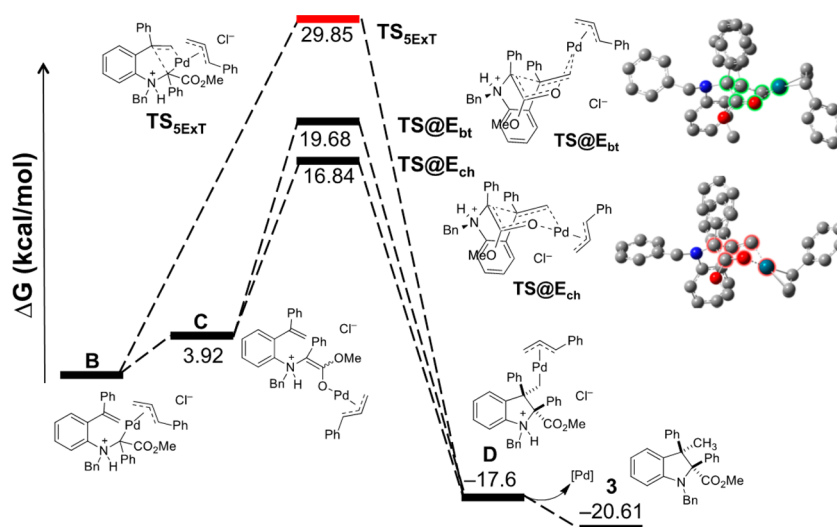
X with the lowest overall activation barriers (19.11 kcal/mol, **Figure S1**). Subsequent cyclization could follow two possible pathways: (1) Heck type of cyclization and (2) metallo–ene kind of reaction. **Figure 1** shows the free energy profiles calculated for both possible pathways proposed.

As the energy difference between **B** and **C** is very low (3.92 kcal/mol), *N*-ylide **B** isomerizes to intermediate **C** rapidly from which the metallo–ene type of reaction is initiated. Metallo–ene reactions of **C** proceed through six-membered ring transition states of both chairlike and boatlike conformations (TS@E<sub>ch</sub> and TS@E<sub>bt</sub>) where both of them predominantly result in both phenyl groups (Ph) in the same side, which in turn affords excellent diastereoselectivity. TS@E<sub>ch</sub> has a low activation barrier compared to TS@E<sub>bt</sub>, which is possibly due to the formation of a relatively stable cyclic chairlike six-membered transition state. As suggested by J. M. Knapp et al.,<sup>20</sup> stepwise mechanistic pathways initiated from both **B** and **C** intermediates are also investigated. In complex **C**, attack of the alkene at electrophilic Pd is endothermic in nature by 18.62 kcal/mol with an activation barrier of 20.49 kcal/mol (**Figure S4**, **Supporting Information**). Hence, a stepwise mechanism is unfavorable when compared to a concerted mechanism. On the other hand, transition state TS<sub>SEXT</sub> is associated with Heck-type reaction with *5-exo-trig* mode of cyclization reactions initiated from intermediate **B**, which requires a high activation barrier (29.85 kcal/mol) compared to the metallo–ene reactions (in the range of 16–20 kcal/mol), possibly due to the high steric crowding in the transition state (TS<sub>SEXT</sub>). Thus, these studies reveal that the final cyclization of *N*-ylide **B** and observed diastereoselectivity occurs through the rapid isomerization to **C** and concomitant metallo–ene-type reaction.

## CONCLUSIONS

In conclusion, we have designed and successfully demonstrated an efficient stereoselective palladium-catalyzed intramolecular carbenylative hydroamination of *o*-vinylaniline with  $\alpha$ -diazo-carbonyl compounds. A broad substrate scope has been established to afford various tri- and tetrasubstituted indolines in good yields with excellent diastereoselectivity. Important features of the present methodology include the construction of two contiguous quaternary carbon centers via the formation of C–N and C–C bonds in a single operation, wide functional





**Figure 1.** Energy profile diagram for the cyclization of *N*-ylide **B** to indoline **3**.

group tolerance, excellent diastereoselectivity, high atom and step economy, trapping without the assistance of any additives, and gram-scale synthesis. Furthermore, the reaction mechanism has been explored by a combination of experimental and DFT studies, which unveiled the initial formation of *N*-ylide followed by cyclization via a metallo–ene-type reaction involving a six-membered cyclic transition state, which also establishes the observed diastereoselectivity.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b02072.

Experimental details, characterization data, geometries of optimized structure/transition states, and  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of isolated compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) (a) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2007. (b) Dötz, K. H. *Metal Carbenes in Organic Synthesis*. In *Topics in Organometallic Chemistry*; Springer-Verlag: Berlin, 2004; Vol. 13.
- (2) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697–756.

- (3) Doyle, M. P.; McKerver, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998.

- (4) (a) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050. (b) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051–3060.

- (5) (a) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857–1869. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (c) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704–24. (d) Gillingham, D.; Fei, N. *Chem. Soc. Rev.* **2013**, *42*, 4918–4931.

- (6) (a) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341–2372. (b) Zhang, Y.; Wang, J. *Coord. Chem. Rev.* **2010**, *254*, 941–953. (c) West, F. G. Rearrangement Processes of Oxonium and Ammonium Ylides Formed by Rhodium(II)-Catalyzed Carbene Transfer. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 417.

- (7) (a) Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2011**, *2011*, 1015–1026. (b) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486–7500. (c) Gutiérrez-Bonet, Á.; Juliá-Hernández, F.; de Luis, B.; Martín, R. J. *Am. Chem. Soc.* **2016**, *138*, 6384–6387.

- (8) (a) Xia, Y.; Feng, S.; Liu, Z.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 7891–7894. (b) Jia, S.; Xing, D.; Zhang, D.; Hu, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 13098–13101. (c) Urabe, F.; Miyamoto, S.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2014**, *16*, 1004–1007. (d) Xiao, Q.; Wang, B.; Tian, L.; Yang, Y.; Ma, J.; Zhang, Y.; Chen, S.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 9305–9308. (e) Zhou, P.-X.; Zhou, Z.-Z.; Chen, Z.-S.; Ye, Y.-Y.; Zhao, L.-B.; Yang, Y.-F.; Xia, X.-F.; Luo, J.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, *49*, 561–563. (f) Qiu, L.; Guo, X.; Ma, C.; Qiu, H.; Liu, S.; Yang, L.; Hu, W. *Chem. Commun.* **2014**, *50*, 2196–2198. (g) Chen, Z.-S.; Duan, X.-H.; Zhou, P.-X.; Ali, S.; Luo, J.-Y.; Liang, Y.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 1370–1374.

- (9) (a) Guo, X.; Hu, W. *Acc. Chem. Res.* **2013**, *46*, 2427–2440. (b) Xing, D.; Hu, W. *Tetrahedron Lett.* **2014**, *55*, 777–783.

- (10) (a) Zhou, C.-Y.; Wang, J.-C.; Wei, J.; Xu, Z.-J.; Guo, Z.; Low, K.-H.; Che, C.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11376–11380. (b) Lu, C.-D.; Liu, H.; Chen, Z.-Y.; Hu, W.-H.; Mi, A.-Q. *Org. Lett.* **2005**, *7*, 83–86. (c) Jiang, J.; Guan, X.; Liu, S.; Ren, B.; Ma, X.; Guo, X.; Lv, F.; Wu, X.; Hu, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 1539–1542. (d) Jing, C.; Xing, D.; Hu, W. *Chem. Commun.* **2014**, *50*, 951–953. (e) Nicolle, S. M.; Lewis, W.; Hayes, C. J.; Moody, C. J. *Angew. Chem.* **2015**, *127*, 8605–8609.

- (11) (a) Qiu, H.; Li, M.; Jiang, L.-Q.; Lv, F.-P.; Zan, L.; Zhai, C.-W.; Doyle, M. P.; Hu, W.-H. *Nat. Chem.* **2012**, *4*, 733–738. (b) Jiang, J.; Xu, H.-D.; Xi, J.-B.; Ren, B.-Y.; Lv, F.-P.; Guo, X.; Jiang, L.-Q.; Zhang, Z.-Y.; Hu, W.-H. *J. Am. Chem. Soc.* **2011**, *133*, 8428–8431. (c) Hu, W.;

Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Hu, J.; Yang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782–7783. (d) Wang, Y.; Zhu, Y.; Chen, Z.; Mi, A.; Hu, W.; Doyle, M. P. *Org. Lett.* **2003**, *5*, 3923–3926. (e) Tang, M.; Xing, D.; Huang, H.; Hu, W. *Chem. Commun.* **2015**, *51*, 10612–10615.

(12) (a) Jing, C.; Xing, D.; Qian, Y.; Shi, T.; Zhao, Y.; Hu, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 9289–9292. (b) Chen, D.-F.; Zhao, F.; Hu, Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 10763–10767. (c) Jiang, L.; Xu, R.; Kang, Z.; Feng, Y.; Sun, F.; Hu, W. *J. Org. Chem.* **2014**, *79*, 8440–8446. (d) Ma, X.; Jiang, J.; Lv, S.; Yao, W.; Yang, Y.; Liu, S.; Xia, F.; Hu, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 13136–13139.

(13) (a) Bräse, S.; Meijere, A. d. Cross-Coupling of Organyl Halides with Alkenes—The Heck Reaction. In *Metal-Catalyzed Cross-Coupling Reactions and More*; Wiley-VCH Verlag GmbH & Co. KGaA, 2014; pp 533–663. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2964. (c) Franssen, N. M. G.; Walters, A. J. C.; Reek, J. N. H.; de Bruin, B. *Catal. Sci. Technol.* **2011**, *1*, 153–165.

(14) (a) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986–5009. (b) Wu, X.-F.; Neumann, H.; Spannenberg, A.; Schulz, T.; Jiao, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 14596–14602. (c) Wu, X.-F.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5284–5288.

(15) (a) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181–191. (b) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 2682–2694.

(16) (a) Fattorusso, E.; Tagliatela-Scafati, O. *Modern Alkaloids: Structure, Isolation, Synthesis, and Biology*; Wiley-VCH Verlag GmbH & Co. KGaA, 2008. (b) Serasanambati, M.; Chilakapati, S. R.; Manikonda, P. K.; Kanala, J. R.; Chilakapati, D. R. *Nat. Prod. Res.* **2015**, *29*, 484–490. (c) Chen, J.; Qu, Y.; Wang, D.; Peng, P.; Cai, H.; Gao, Y.; Chen, Z.; Cai, B. *Molecules* **2014**, *19*, 4395–4408.

(17) (a) Ghorai, J.; Anbarasan, P. *J. Org. Chem.* **2015**, *80*, 3455–3461. (b) Yadagiri, D.; Anbarasan, P. *Chem. Sci.* **2015**, *6*, 5847–5852. (c) Rajasekar, S.; Yadagiri, D.; Anbarasan, P. *Chem. - Eur. J.* **2015**, *21*, 17079–17084. (d) Yadagiri, D.; Anbarasan, P. *Org. Lett.* **2014**, *16*, 2510–2513. (e) Yadagiri, D.; Reddy, A. C. S.; Anbarasan, P. *Chem. Sci.* **2016**, *7*, 5934–5938.

(18) CCDC 1438961 contains the supplementary crystallographic data for compound **3m**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

(19) CCDC 1438962 contains the supplementary crystallographic data for compound **3aq**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

(20) Knapp, J. M.; Zhu, J. S.; Tantillo, D. J.; Kurth, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10588–10591.