Rh(II)-Catalysed N^2-Selective Arylation of Benzotriazoles and Indazoles using Quinoid Carbenes via 1,5-H Shift

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Abstract: A Rh(II)-catalyzed highly selective N^2-arylation of benzotriazole is developed with wide scope and good functional group tolerance. The reaction is also extended on indazole and substituted 1,2,3-triazole scaffolds. In addition, late-stage arylation of benzotriazoles tethered with bioactive molecules is realized under the developed conditions. Control experiments and DFT calculations reveal that presumably, the reaction proceeds via nucleophilic addition of N^2 (of 1*H* tautomer) center to metal-carbene followed by 1,5-H shift. This differs from classical X-H insertion into carbene centers and subsequent 1,2-H shift.

Among different azoles, benzotriazole and their derivatives display a wide range of biological and functional material properties.[1] *N*-Arylated benzotriazoles have been found as a key motif in many pharmaceutically important compounds and ultraviolet stabilizers (Figure 1).[2] Therefore, the synthesis of N-arylated benzotriazole is highly desirable, especially in a selective fashion.

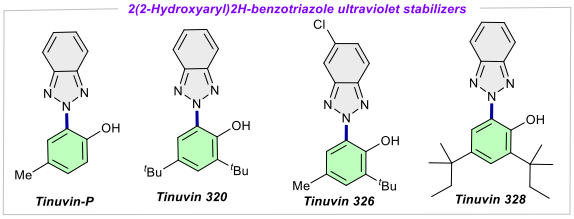
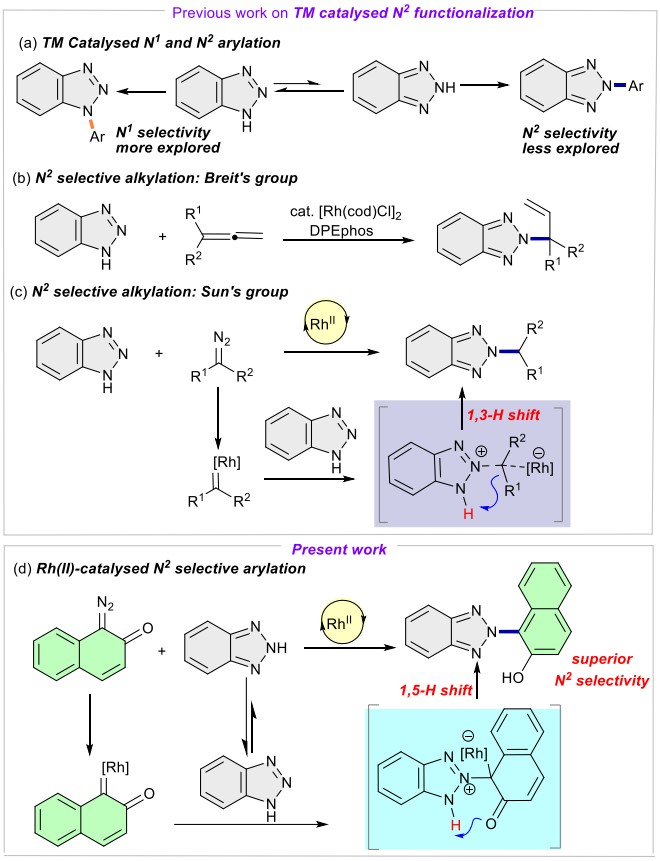


Figure 1: 2(2-Hydroxyaryl)2*H*-benzotriazole as ultraviolet stabilizers

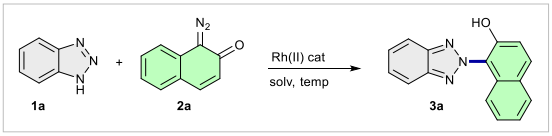
In general, the presence of equilibrium between the 1*H* and 2*H* tautomers[3] of benzotriazole makes the task of selective N^2-functionalizations more troublesome. More importantly, the N^2-functionalizations of benzotriazole are more challenging over non-benzo-1,2,3- triazole due to reduced aromaticity in 2*H* tautomer.[3] Hence, significant progress has been realized in the transition metal catalyzed N^1-functionalizations especially arylation of benzotriazole (Scheme 1a).[4,5] Recently transition metals especially rhodium catalyzed N^2-selective functionalizations were explored.[6,7] In a pioneering work, Breit's group established a ligand-controlled Rh(I)-catalyzed N^2-alkylation of benzotriazole using allene as a coupling partner (Scheme 1b).[7a]



Scheme 1 N^2 Selective arylation of benzotriazole.

In another recent elegant work, Sun's group achieved a site-selective N^2-alkylation of benzotriazole using aryl diazoacetate via a non-classical 1,3-H shift pathway (Scheme 1c).[7b] However, the attempt to obtain transition metal-catalyzed N^2-selective arylation of benzotriazole led to 1:1 mixture of N^1 and N^2-aryl isomers.[8] To the best of our knowledge, there is no previously known literature on transition metal-catalyzed N^2-selective arylation of challenging benzotriazole scaffolds. Since the last few years, diazo compounds[9] especially diazoquinones have been strategically explored for various C-H arylations.[10,11] However, the N-H arylations using the quinoid carbene species are scarce.[12] Driven by our early interests in the insertion of quinoid carbenes, especially for the directed CH-arylations[13] and NH-arylations[14], we hypothesized that the control of N^2-arylation over N^1-arylation might be possible with quinoid carbene species as the catalyst might differentiate the energy difference between N^2 and N^1 intermediate. Herein we describe the Rh(II)-catalyzed highly regioselective N^2-arylation using diazonaphthoquinone as a coupling partner via quinoid carbene formation based on a combination of experimental and DFT studies (Scheme 1d). Notably, DFT calculations indicate that this unprecedented N^2-arylation proceeds through the promising route of 1,5-proton shift via the 1H tautomer or via an uncommon 1,4-proton shift pathway through the less stable 2H tautomer. However, the possibility of a classical X-H bond insertion into metal-carbene via 1,2-proton shift is bleak.[15]

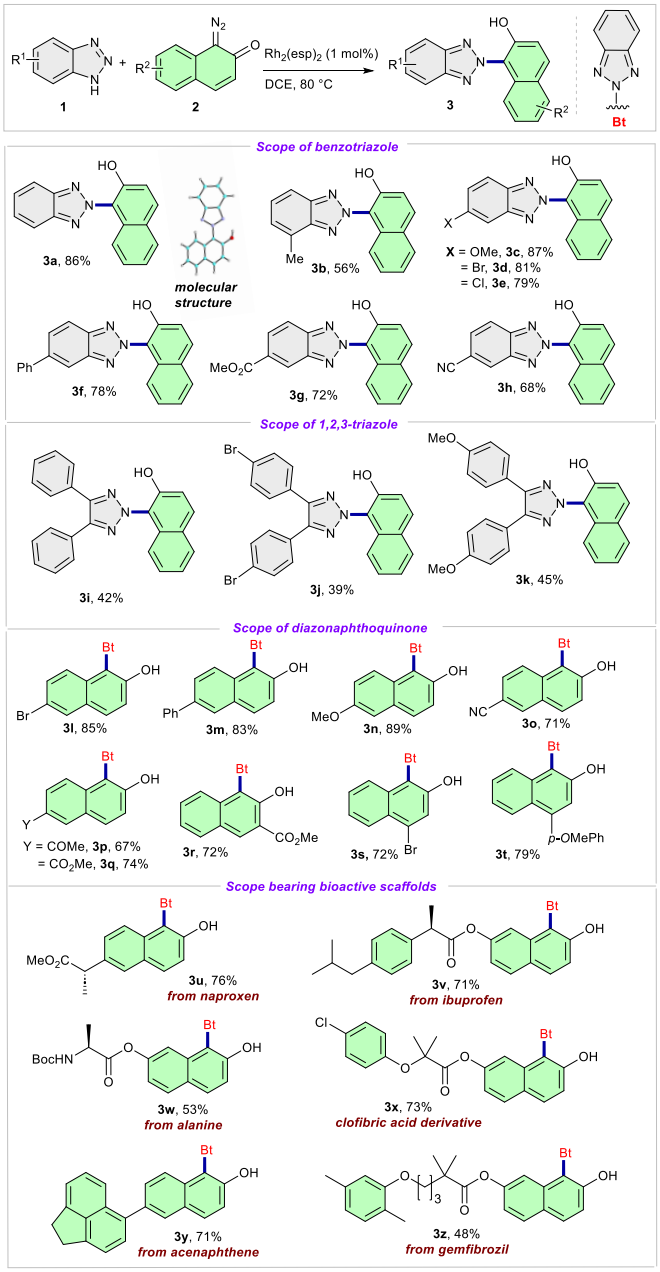
Table 1 Optimization of benzotriazole arylation with diazonaphthoquinone[a]



entries	cat (mol%)	solv (temp)	N^2/N^1 [b]	yield (%)[c]
1	$Rh_2(OAc)_4$ (1)	DCE (50 °C)	-	trace
2	$Rh_2(Oct)_4$ (1)	DCE (50 °C)	-	trace
3	$Rh_2(esp)_2$ (1)	DCE (50 °C)	>99:1	48
4	$Rh_2(esp)_2$ (1)	DCM (50 °C)	>99:1	36
5	$Rh_2(esp)_2$ (1)	toluene (50 °C)	>99:1	38
6	$Rh_2(esp)_2$ (1)	MeCN (50 °C)	4:3	33
7	$Rh_2(esp)_2$ (1)	dioxane (50 °C)	5:1	26
8	$Rh_2(esp)_2$ (1)	MeOH (50 °C)	-	-
9	$Rh_2(esp)_2$ (1)	DCE (40 °C)	>99:1	41
10	$Rh_2(esp)_2$ (1)	DCE (60 °C)	>99:1	73
11	$Rh_2(esp)_2$ (1)	DCE (70 °C)	>99:1	83
12[d,e]	**$Rh_2(esp)_2$ (1)**	**DCE (80 °C)**	**>99:1**	**91 (86)**
13	$Rh_2(esp)_2$ (1)	DCE (90 °C)	>99:1	84
14	$Rh_2(esp)_2$ (0.5)	DCE (80 °C)	>99:1	64

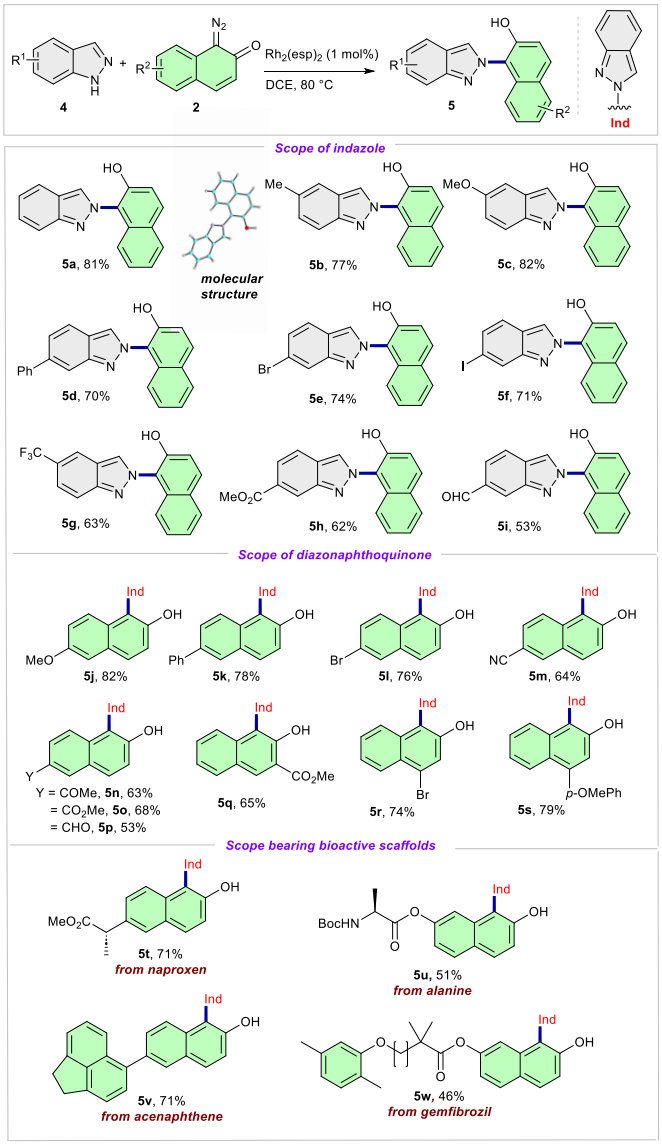
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), Rh-catalyst (1 mol%), solvent (0.1 M), 12 h. [b]Determined by ^{1}H NMR analysis. [c]Yield was calculated by ^{1}H NMR using 1,3,5 trimethoxybenzene as standard. [d]Isolated yield is in parenthesis. [e]Reaction time is 6 h.

Our early studies commenced with benzotriazole (**1a**) and diazonaphthoquinone (**2a**) as an arylating agent under Rh(II)-catalysts in DCE at 50 °C (Table 1). The initial attempts with $Rh_2(OAc)_4$ and $Rh_2(Oct)_4$ were unsuccessful (Table 1, entries 1-2). Gratifyingly, when 1 mol% $Rh_2(esp)_2$ was used as the catalyst, the desired arylated benzotriazole **3a** was formed in excellent N^2-selectivity with reasonable yield (Table 1, entry 3). Further screening of solvents did not improve the yield of the desired product and site selectivity (Table 1, entries 4-8). Moreover, the yield of product **3a** was reduced under lower reaction temperature (Table 1, entry 9) albeit with high N^2 selectivity. To improve the yield, the reaction was carried out under elevated reaction temperature (Table 1, entries 10-13). Gladly, the best yield of the desired benzotriazole arylated product **3a** was obtained in 86% with very high N^2 selectivity under 1 mol% $Rh_2(esp)_2$ catalyst (Table 1, entry 12). Further decrease in the catalyst loading, reduced the formation of the desired product (Table 1, entry 14).



Scheme 2 Scope of N^2-arylated benzotriazole. **1** (0.2 mmol), **2** (0.24 mmol), $Rh_2(esp)_2$ (1 mol%), DCE (1 ml), 80 °C, 12 h.

After having the optimization conditions in our hands, we explored the scope for N^2-arylated benzotriazoles. Initially, we explored the scope of different benzotriazoles. Alkyl substitution at the C7 position of benzotriazole core provided a moderate yield of the desired product. Presumably, the bulk at this position lowered the yield (Scheme 2, **3b**). Other electron-rich substitution like the OMe group provided an excellent yield of the desired product (Scheme 2, **3c**). Halide substitutions were accommodated during the reaction keeping the window for further transformations (Scheme 2, **3d**-**3e**).

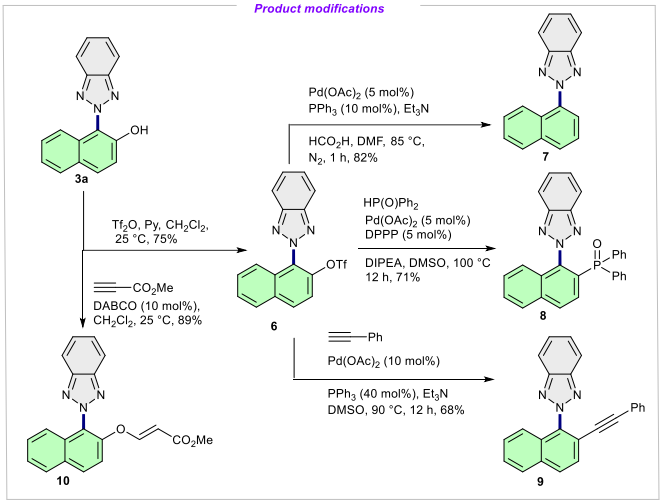


Scheme 3 Scope of N^2-arylated indazole. **1** (0.2 mmol), **2** (0.24 mmol), $Rh_2(esp)_2$ (1 mol%), DCE (1 ml), 80 °C, 12 h.

Extended conjugating Ph group and electron-withdrawing functionalities like ester and cyano groups also afforded the desired products in very good yields (Scheme 2, **3f**-**3h**). Notably, another important class of triazole i.e. 1,2,3-triazole was also explored for N^2-arylation under our developed conditions. We were glad to see that this class of compounds also afforded N^2-arylated products in synthetically acceptable yields (Scheme 2, **3i**-**3k**). Next, we wanted to screen the scope of electronically and sterically variable diazonaphthoquinones. Further, the reaction was compatible with a broad range of functional groups at both the ring of diazonaphthoquinone (Scheme 2, **3l**-**3t**). We found that diazonaphthoquinone featuring halide, electron-donating, and electron-withdrawing groups underwent the N^2-naphtholation smoothly. Moreover, the generality of the N^2-arylation was tested using different pharmaceutically and biologically important molecules like naproxen (Scheme 2, **3u**), ibuprofen (Scheme 2, **3v**), alanine (Scheme 2, **3w**), clofibric acid (Scheme 2, **3x**), acenaphthene (Scheme 2, **3y**), and gemfibrozil (Scheme 2, **3z**) tethering diazonaphthoquinone. This showcases the generality of the developed method. The structure of **3a** was unequivocally confirmed *via* single-crystal X-ray analysis.

N^2-arylated indazoles are an important class of azoles that exhibit a wide range of biological activities.[16] Therefore, steady progress was realized in developing this scaffold under transition metal catalysis.[17] However,

direct N^2 arylation under transition metal catalyzed conditions is limited. Especially, there was no success in the bulky aryl group introduction at the N^2-position.[17e] We hypothesized that our developed N^2-selective naphtholation on benzotriazole scaffolds using quinoid carbene chemistry could be extended to indazole as well. Gratifyingly, indazole provided N^2-arylated product in excellent yield under the developed conditions (Scheme 3, **5a**). Next, electron-rich functionalities afforded very good yields of the desired products (Scheme 3, **5b**-**5d**). Halogens were accommodated during the reaction (Scheme 3, **5e**-**5f**). Notably, the electron-withdrawing groups were also with decent yields (Scheme 3, **5g**-**5i**). Next, we explored the scope of the diazonaphthoquinones. The electronic and steric nature of the versatile functionalities did not impede the reactivity of the substrates towards the naphtholation procedure (Scheme 3, **5j**-**5s**).

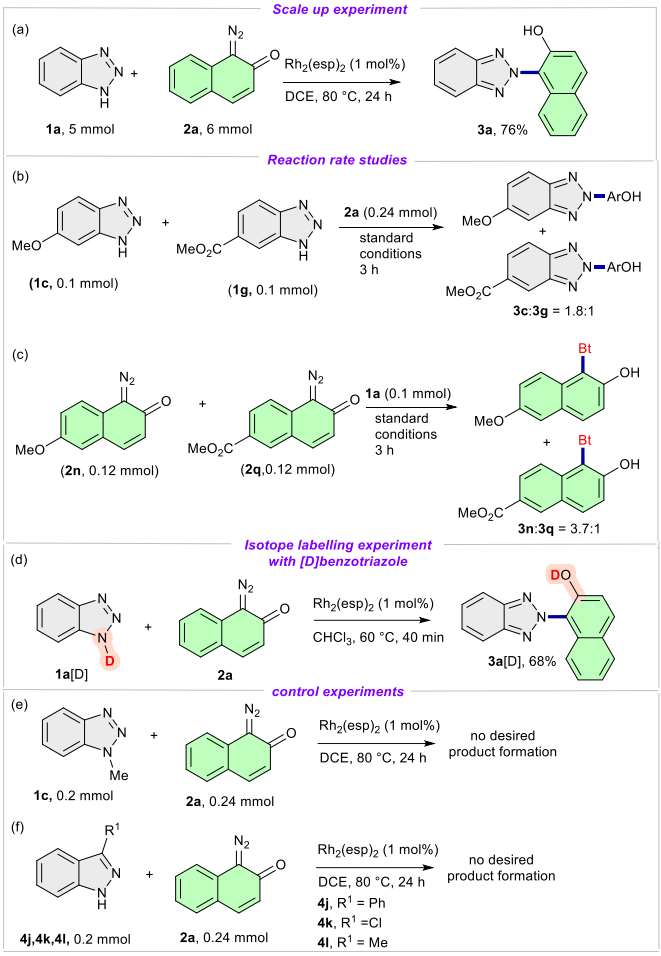


Scheme 4 Product modifications

Further, to demonstrate the developed method's robustness, it was extended with diazonaphthoquinones tethered with bioactive molecules like naproxen (Scheme 3, **5t**), alanine (Scheme 3, **5u**), acenaphthene (Scheme 3, **5v**), gemfibrozil (Scheme 3, **5w**) to provide corresponding N^2-arylated indazole scaffolds. Finally, the structure of the N^2-arylated indazole was undoubtedly confirmed through single-crystal X-ray analysis of compound **5a**.

The transformation ability of the synthesized benzotriazole-attached naphthol moiety led us to carry out a series of functional group modifications (Scheme 4). The hydroxy functionality of naphthol moiety was converted to the corresponding triflate derivative **6**. Further, this triflate functionality was removed under Pd(0)-catalyzed conditions to obtain compound **7** in 82% yield. Furthermore, compound **6** was transformed into its phosphine oxide **8**. Next, alkyne derivative **9** was obtained from the triflate compound **6** under Sonogashira-type coupling**.** Finally, naphthol moiety **6** was converted to its alkoxy acrylate derivative **10** with methyl propiolate in 89% yield.

To check the practical applicability, the N^2-arylation was scaled up in a 5 mmol scale to afford **3a** in 76% yield (Scheme 5a). Next, a competition between electron-rich OMe and electron-withdrawing CO_2Me groups at the C6-position of benzotriazole was executed to reveal that electron-donating **1c** reacts marginally better over the electron-deficient **1g** (Scheme 5b).



Scheme 5 Preliminary mechanistic studies.

Further, electron-rich diazonaphthoquinone **2q** reacts better over electron-deficient diazonaphthoquinone **2n** with benzotriazole under the optimized conditions (Scheme 5c). Furthermore, to know the pathway for proton transfer from benzotriazole N1-H to naphthol oxygen center, an important control experiment on deuterium transfer was carried out (Scheme 5d). N^1-[D]benzotriazole was treated with diazonaphthoquinone **2a** to result in the N^2-[D]naphtholated benzotriazole (see supporting information for more details). This proves that the proton of NH transfers from the benzotriazole moiety to the naphthol oxygen center. When the benzotriazole N-H was protected with methyl group, there was no desired product formation under standard conditions (Scheme 5e). This indicates that the important role of free N-H functionality for the successful transformation. Further, the C3-substituted indazoles (**4j**, **4k or 4l**) were exposed under optimized conditions to offer no desired product (Scheme 5f). Presumably, the steric crowding at that position prohibits the formation of desired product.

To get more insight into this N^2 selective naphtholation, DFT calculations were performed at B3LYP-D3/Def2TZVP/CPCM level of theory. The relevant steps of the catalytic cycle with the potential energies of transition states and intermediates are represented in Figure 2 (see supporting information for more details). Based on control experiments and previous related reports,[7b, 18] we hypothesize that the rhodium-carbenoid species **INT1** is formed from extrusion of N_2 from the diazonaphthoquinone **2a** on coordination of the Rh(II)-catalyst with an energy barrier of 16.1 kcal/mol (Figure 2). This nitrogen extrusion step is endoergic by 4.1 kcal/mol, similar to predictions by Hansen and others.[18] Next, we wanted to check the selective insertion of N^1 or N^2 center to quinoid carbene. Notably, as shown in Figure S3, the tautomerism of 1H-benzotriazole (**1a**) to 2H-benzotriazole (**1a'**) proceeds

through a dimerization step, occurring at an energetic expense of 17.5 kcal/mol, with an overall endergonicity of >5 kcal/mol for the 2H-tautomer. This suggests the greater abundance of **1a** over **1a'** in an equilibrium mixture. Nevertheless, we have explored the mechanistic steps emanating from **1a'** as well to gain clarity on the mechanism and selectivity. We explored both 1H and 2H direct nucleophilic attacks on the metal-carbenoid center. While the 2H tautomer direct attack through **TSN^{2}H$_{direct}$** is a concerted process of nucleophilic addition and proton exchange, the 1H tautomer direct attack leads to a step-wise process via **TSN^{1}H$_{direct}$** and **TS3**. Notably, the 1H direct attack takes place at barriers of 4.8 and 2.4 kcal/mol for the nucleophilic addition and proton transfer steps, respectively. However, **TSN^{2}H$_{direct}$** occurring through a reasonable energetic expense of 14.4 kcal/mol cannot be ruled out under the experimental conditions, albeit the preference for a 1H direct attack is greater. Thereafter, we explored the possibility of N^2 attack with 1H tautomer (**TSN^{1}H$_{N2nuc}$**) and N1 attack with 2H tautomer (**TSN^{2}H$_{N1nuc}$**). Interestingly, these led to barrierless reaction steps with reference to the starting compounds, **RC1** and the benzotriazole. Linear transit scans of the N-C(carbene) distance starting from local intermediates with a slightly sterically less-hindered orientation of the ligand, **RCN^{1}H$_{N2nuc}$** for N^2 nucleophilic attack and **RCN^{2}H$_{N1nuc}$** for N^1 nucleophilic attack, leading to N^2 and N^1 products, **3a[Rh]** and **3a'[Rh]**, respectively, were then analyzed (Figure S4). A careful investigation reveals that while **TSN^{1}H$_{N2nuc}$** shows $\Delta E^{\ddagger}$ = 0.0 kcal/mol, **TSN^{2}H$_{N1nuc}$** must overcome $\Delta E^{\ddagger}$ = 0.8 kcal/mol, which might explain the observed regio-selectivity. Furthermore, as shown in Figure 2, the C-N distances in **TSN^{1}H$_{N2nuc}$** (2.53 Å) and **TSN^{2}H$_{N1nuc}$** (2.46 Å) are apparently much longer than those found in **TSN^{1}H$_{direct}$** (2.09 Å) and **TSN^{2}H$_{direct}$** (1.96 Å), indicating that the two most favorable transition states are observed at an early stage. The relative kinetics of **TSN^{2}H$_{N1nuc}$** and **TSN^{1}H$_{N2nuc}$** ($\Delta\Delta E^{\ddagger}$ = 0.8 kcal/mol), in principle captures the relative stability of the 1H and 2H tautomer, as well as the difference in energy of the 1H and 2H products (Figure 2, Figure S4). Hence, one may argue that N^2 selectivity is both kinetically and thermodynamically controlled.

Additionally, the steric factor might also play an important role in achieving N^2-selectivity. The less sterically

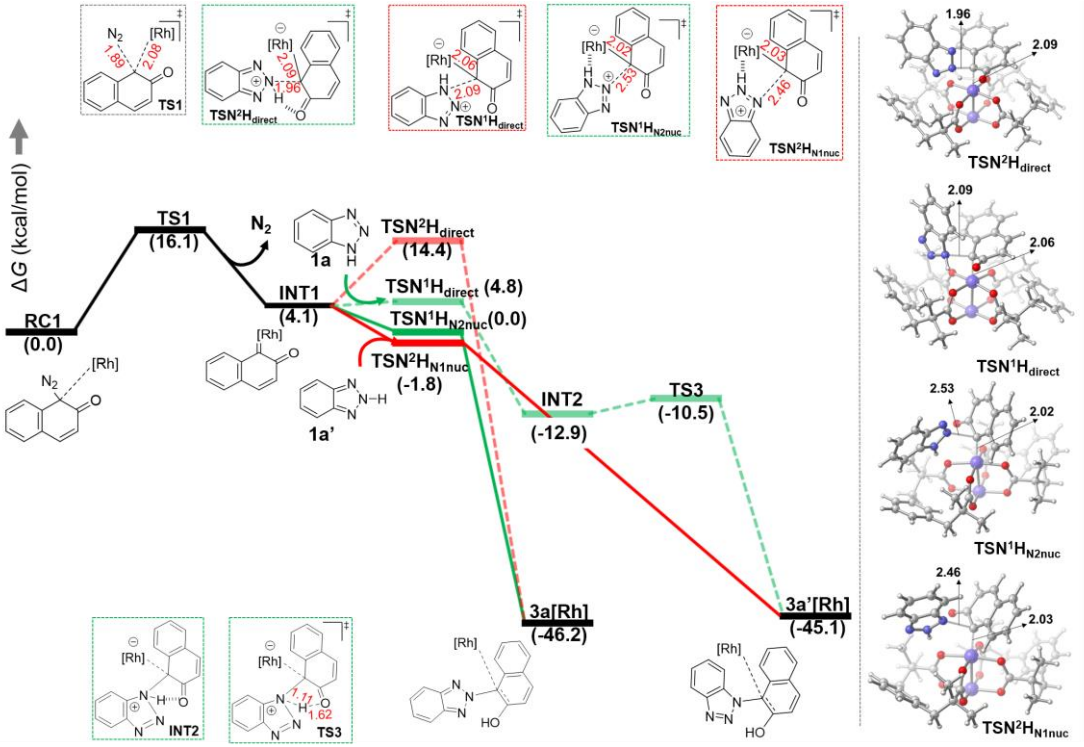


Figure 2. Relative Gibbs free energy profile at B3LYP-D3/Def2TZVP/CPCM in kcal/mol. Reaction paths with **1a** (N^1 tautomer) and **1a'** (N^2 tautomer) are shown in green and red profiles, respectively. Optimized geometries at B3LYP-D3/Def2SVP/W06 level of theory are shown. Distances shown are in units of Å. Color codes: Rh (purple), N (blue), C (grey), H (white), O (red).

hindered N^2 center is more feasible for the nucleophilic attack at the bulky electrophilic rhodium-carbene center. Indeed, the insertion of N^2 center of the 1H-tautomer to rhodium in the quinoid carbene center and subsequent proton shifts demonstrates an overall barrier greater than 25 kcal/mol, indicating that classical migratory insertion might not be a possibility in this reaction (Figure S5).[6b] Further, the observation of weak H-bonding between the N^1H functionality with the carboxylate groups of esp ligand in **RCN^{1}H$_{N2nuc}$** (2.03 Å, Figure S4) leading to favorable N^2 attack might explain the necessity of an unsubstituted NH.

In conclusion, a Rh(II)-catalyzed highly selective N^2-arylation of benzotriazole, triazole, and indazole derivatives was developed using diazonaphthoquinone as a coupling partner. The reaction was extended with a wide substrate scope and functional group tolerance. Late-stage functionalizations of complex bioactive molecules were also studied successfully. A notable mechanism was proposed that differed from the classical mechanism of N-H insertion to metal-carbene and following 1,2 proton transfer. DFT studies suggested that presumably, the reaction pathway followed the initial nucleophilic attack of N^2-center of 1H-benzotriazole to quinoid carbene and subsequent 1,5-proton shift from N^1-H to oxygen center to afford the N^2-arylated benzotriazole and related derivatives.

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Author Contributions

S.S and R.S. conceived and designed the experiments. S.S., S.P. and A.D. performed the experiments. S.B. and L.R. did the DFT computation. S.S., R.S., S.B. and L.R. wrote the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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