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COPPER-CATALYZED β-IODOVINYLATION OF AZOLE AND PYRROLE DERIVATIVES

Simon Ricard, François Ladouceur, Guillaume Couture, and Benoit Daoust*

Department of Chemistry, Biochemistry and Physics, University of Quebec in Trois-Rivieres, CP. 500, Trois-Rivieres, Quebec, Canada G9A 5H7. Email address: Benoit.Daoust@uqtr.ca.

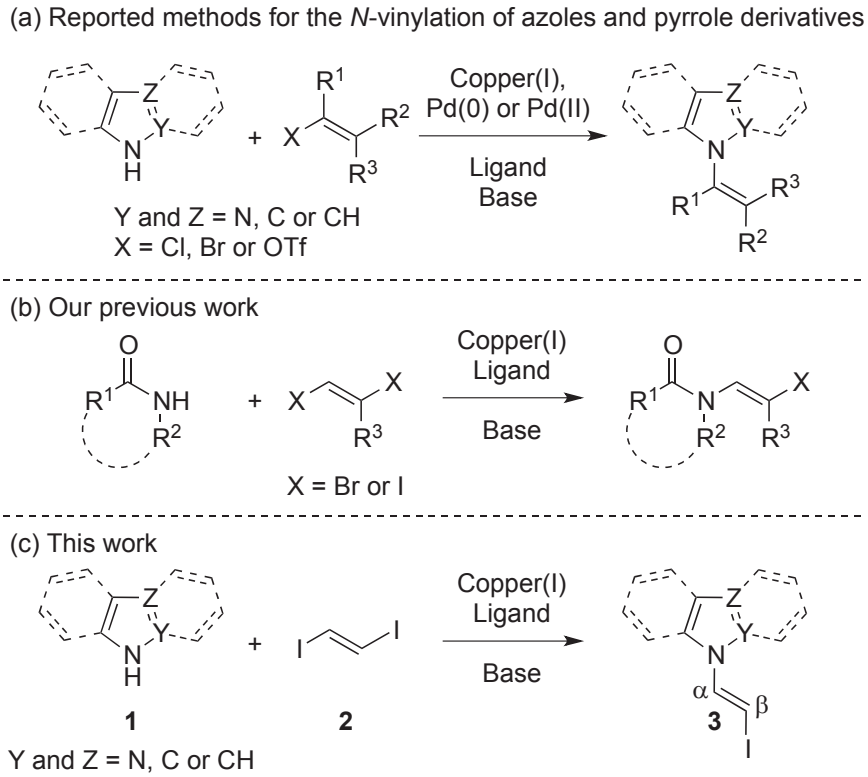
Abstract – Herein is described an efficient copper-catalyzed synthesis of β-iodovinyl-azole and β-iodovinyl-pyrrole derivatives using (*E*)-1,2-diiodoethene which was efficiently applied to azole and pyrrole derivatives in both organic and hydro-organic medium to afford the corresponding β-iodovinylated adducts in up to excellent yields with complete stereocontrol. These nitrogenated vinyl iodides can be further functionalized into disubstituted olefins through various metal catalyzed coupling reactions.

INTRODUCTION

Azole and pyrrole derivatives are found abundantly in nature as key metabolites (e.g. histamine, histidine, cobalamin, tryptophan and serotonin) and as natural products (e.g. archazolids, aplicyanins, β-carbolines and vinblastine).[1] In addition, a number of these compounds has been found to display anticancer and antifungal activities.[2] Moreover, *N*-vinyl-azoles are important building blocks in both pharmacology and material science.[3] Consequently, there is a need for efficient methods to synthesize and modify these ubiquitous entities.

Metal-catalyzed *N*-arylation of azole and pyrrole derivatives received a lot of attention in the past decade.[3a,4] However, very few examples were reported for the *N*-vinylation of these substrates (Scheme 1a).[3,5] Additionally, further functionalization of these vinylated adducts appears to be tedious,[6a,c,7a] often leads to isomerization issues[6a,c–f] and generally has a very limited scope.[6b,e,g–i] To overcomethese problems, Pawluć's group took advantage of the iodovinyl moiety of β-iodovinylcarbazole to perform Suzuki, Sonogashira and Heck couplings.[7] Note that only β-iodovinylcarbazole (**3c**) was submitted to

those transformations due to the lack of efficient methods to synthesize β-iodovinyl-azole and β-iodovinyl-pyrrole derivatives.



Scheme 1. Reported methods for the *N*-vinylation of azole and pyrrole derivatives

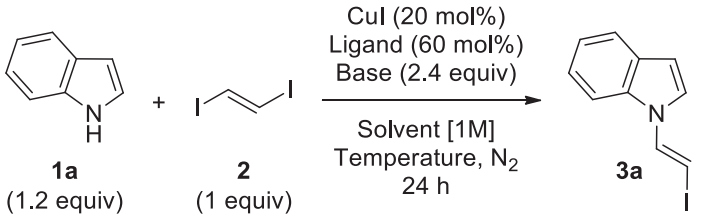
Since 2008, our group developed an expertise on the copper-catalyzed β-halovinylation of amide derivatives (Scheme 1b).[8] We demonstrated that β-halovinyl-amide derivatives could be prepared in good to excellent yields with complete regio and stereocontrol while avoiding the production of any bis-coupling adduct. In light of our expertise, we decided to expand the scope of these β-halovinylation reactions to azole and pyrrole derivatives **1** (Scheme 1c). We envisioned that β-iodovinyl-azole and β-iodovinyl-pyrrole derivatives **3** could be obtained via copper(I)-catalyzed coupling of (*E*)-1,2-diiodoethene (**2**) with azole and pyrrole derivatives **1** respectively.

RESULTS AND DISCUSSION

We began our work by optimizing the reaction conditions for the β-iodovinylation of indole (**1a**) with vinyl diiodide **2** using the conditions that we previously reported for the β-iodovinylation of amide derivatives (i.e. 1 equiv vinyl diiodide, 1.2 equiv amide derivative, 20 mol% CuI, 60 mol% DMEDA and 2.4 equiv Cs_2CO_3 in 1,4-dioxane [1M] at 55 °C).[8b] From those reported conditions, the ligand, base and solvent were optimized independently for the β-iodovinylation of indole (**1a**), and the results of this optimization are reported in Table 1. Note that pyrrole was initially selected as our model substrate since

it is the simplest pyrrole derivative but was rapidly discarded due to its air and light sensitivity as well as its sluggish reactivity.

Table 1. Optimization of the reaction conditions for the β-iodovinylation of indole (**1a**) with vinyl diiodide **2**

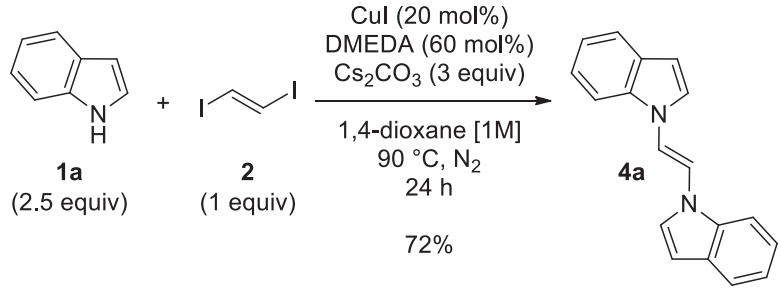


Entry	Ligand	Base	Solvent	Temperature	Yield[a] (Isolated **3a**)	Recovery of **1a**[a]
1	**DMEDA**	Cs_2CO_3	1,4-dioxane	55 °C	85%	6%
2	**EDA**	Cs_2CO_3	1,4-dioxane	55 °C	38%	27%
3	**glycine**	Cs_2CO_3	1,4-dioxane	55 °C	67%	9%
4	**acac**	Cs_2CO_3	1,4-dioxane	55 °C	33%	28%
5	DMEDA	**K_2CO_3**	1,4-dioxane	55 °C	40%	26%
6	DMEDA	**K_3PO_4**	1,4-dioxane	55 °C	72%	17%
7	DMEDA	**KOH**	1,4-dioxane	55 °C	61%	25%
8	DMEDA	**pyridine**	1,4-dioxane	55 °C	<5%	40%
9	DMEDA	Cs_2CO_3	**toluene**	55 °C	73%	0%
10	DMEDA	Cs_2CO_3	**DMSO**	55 °C	23%	49%
11	DMEDA	Cs_2CO_3	**water**	55 °C	41%	27%
12	DMEDA	Cs_2CO_3	1,4-dioxane	**90 °C**	68%	0%
13	DMEDA	Cs_2CO_3	1,4-dioxane	**25 °C**	91%	2%
14[b]	DMEDA	Cs_2CO_3	1,4-dioxane	**25 °C**	>99% (95%)	0%

DMEDA = *N,N'*-dimethylethylenediamine. EDA = ethylenediamine. acac = acetylacetone. [a]Yields and recoveries were determined by GCMS using DMAP as standard. [b]The reaction was carried out using 1 equiv of indole (**1a**) and 1.2 equiv of vinyl diiodide **2**.

The coupling between **1a** and vinyl diiodide **2** using the aforementioned conditions afforded the desired product **3a** in a very good yield (Table 1, entry 1). Permuting DMEDA for EDA, glycine or acac led to significantly lower yields along with higher recoveries of **1a** (Table 1, entries 2–4). Substituting cesium carbonate for potassium carbonate, potassium phosphate or potassium hydroxide also provided lower yields of **3a** while using pyridine as base produced only traces of the desired product (Table 1, entries 5–8). Replacing 1,4-dioxane with toluene had little impact on the transformation (73% vs 85%), but when the reaction was carried out in DMSO, adduct **3a** was obtained in poor yield (Table 1, entries 9–10). Surprisingly, using water as solvent for this coupling reaction afforded **3a** in 41% yield (Table 1, entry 11).

Since the tested interchanges of ligand, base and solvent did not offer any significant improvement on the β-iodovinylation of indole (**1a**), we investigated the effect of the temperature on this transformation. We performed the reaction at 90 °C, which led to a lower yield than at 55 °C (68% versus 85%) along with complete consumption of **1a** (Table 1, entry 12). Analysis of the crude mixture by GC-MS showed, for the first time, trace amounts of a bis-coupling adduct which could have been produced in our conditions via a double coupling process due to the presence of a slight excess of indole (**1a**) (i.e. 1.2 equiv). To confirm this hypothesis, the reaction was carried out under the same conditions but with a larger excess of **1a** (i.e. 2.5 vs 1.2 equiv) which led to diadduct **4a** in good yield (Scheme 2).



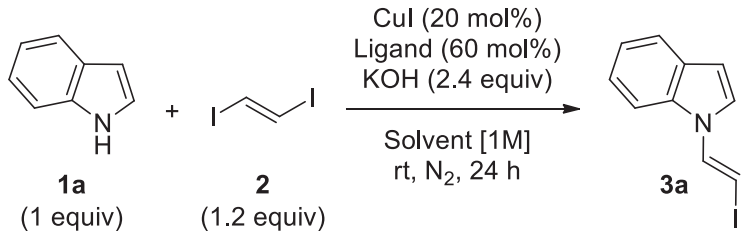
Scheme 2. Formation of diadduct **4a** using an excess of indole (**1a**)

On the other side, performing the reaction at 25 °C completely averted the formation of diadduct **4a** and even slightly improved the yield of the transformation (91% vs 85%) (Table 1, entry 13). At this temperature, when indole (**1a**) was used as the limiting reagent, the reaction proceeded quantitatively and adduct **3a** could be isolated in excellent yield (Table 1, entry 14).

Though highly satisfied with this optimization, we were still intrigued by the efficiency of the β-iodovinylation of indole (**1a**) in water (Table 1, entry 11) since water systematically appeared to be an unsuitable solvent in our previously reported copper-catalyzed β-halovinylation reactions.[8] Development of efficient and versatile conditions to perform copper-catalyzed vinylation and arylation reactions in aqueous media are scarce, very recent, and generally require an extensive optimization process due to the limited water solubility of organic compounds.[9]

Encouraged by our first result in water, we then initiate a second optimization phase to develop a set of conditions to perform the β-iodovinylation of indole (**1a**) in aqueous media. We undertook this work using our previously optimized conditions for the β-iodovinylation of indole (**1a**) in an organic medium (Table 1, entry 14), but we compelled ourselves to use potassium hydroxide as base in addition to use an aqueous medium as solvent to obtain greener and more sustainable conditions. The results of this optimization are reported in Table 2.

Table 2. Optimization of the reaction conditions for the β-iodovinylation of indole (**1a**) with vinyl diiodide **2** in aqueous media



Entry	Ligand	Solvent	Yield[a] (Isolated **3a**)	Recovery of **1a**[a]
1	**DMEDA**	H_2O	49%	21%
2	**EDA**	H_2O	42%	42%
3	**glycine**	H_2O	30%	19%
4	**acac**	H_2O	19%	49%
5	DMEDA	**MeOH/H_2O (1:1)**	59%	10%
6	DMEDA	**EtOH/H_2O (1:1)**	72%	9%
7	DMEDA	**THF/H_2O (1:1)**	95%	0%
8	DMEDA	**THF/H_2O (1:10)**	>99% (94%)	0%

DMEDA = *N,N'*-dimethylethylenediamine. EDA = ethylenediamine. acac = acetylacetone. [a]Yields and recoveries were determined by GCMS using DMAP as standard.

The coupling between **1a** and vinyl diiodide **2** using our self-imposed conditions afforded the desired product **3a** in a fair yield with partial recovery of **1a** despite the highly heterogeneous character of the reaction (Table 2, entry 1). Substituting DMEDA for EDA led to a similar result (Table 2, entry 2), while using glycine or acac as ligands led to much lower yields (Table 2, entries 3–4). To improve solvation and homogeneity of the reaction medium, we then decided to use water/cosolvent mixtures (Table 2, entries 5–8). When the reaction was carried out in 1:1 hydro-alcoholic media, the yield in **3a** increased from 49% (pure water) to 59% with methanol and to 72% with ethanol (Table 2, entries 5–6). Gratifyingly, the coupling of indole (**1a**) with vinyl diiodide **2** in a 1:1 THF-water mixture led to β-iodovinylindole (**3a**) in 95% yield (Table 2, entry 7). When carried out in a 1:10 THF-water mixture, the reaction proceeded quantitatively and adduct **3a** could be isolated in excellent yield (Table 2, entry 8).

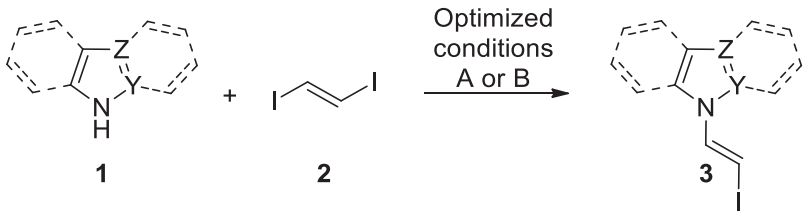
Our optimized reaction conditions for the β-iodovinylation of indole (**1a**) in organic and hydro-organic media are respectively:

A) Azole or pyrrole derivative **1** (1 equiv), vinyl diiodide **2** (1.2 equiv), CuI (20 mol%), DMEDA (60 mol%), Cs_2CO_3 (2.4 equiv), 1,4-dioxane [1M], 25 °C, 24 h (Table 1, entry 14)

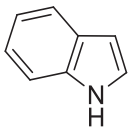
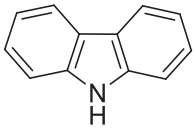
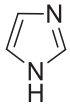
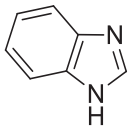
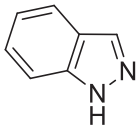
B) Azole or pyrrole derivative **1** (1 equiv), vinyl diiodide **2** (1.2 equiv), CuI (20 mol%), DMEDA (60 mol%), KOH (2.4 equiv), THF:H_2O (1:10) [1M], 25 °C, 24 h (Table 2, entry 8).

Next, we investigated the substrate scope of this transformation by reacting a variety of azole and pyrrole derivatives **1** with vinyl diiodide **2** under both our optimized conditions A and B. These results are reported in Table 3.

Table 3. Substrate scope in the β-iodovinylation of azole and pyrrole derivatives **1**



1 **2** **3**

Entry	Azole or Pyrrole derivative 1	Product 3	Isolated yield Conditions A[a]	Isolated yield Conditions B[b]
1	 **1b**	**3b**	82%	44%
2	 **1a**	**3a**	95%	94%
3	 **1c**	**3c**	81%	68%
4	 **1d**	**3d**	10% 19%[c]	6% 19%[c]
5	 **1e**	**3e**	73%	48%
6	 **1f**	**3f**	75%	52%
7	 **1g**	**3g**	84%	32%

[a]CuI (20 mol%), DMEDA (60 mol%), Cs_2CO_3 (2.4 equiv), 1,4-dioxane [1M], 25 °C, 24 h. [b]CuI (20 mol%), DMEDA (60 mol%), KOH (2.4 equiv), THF:H_2O (1:10) [1M], 25 °C, 24 h. [c]The reaction was carried out at 55 °C.

The tested pyrrole derivatives, pyrrole (**1b**), indole (**1a**) and carbazole (**1c**), coupled smoothly with vinyl diiodide **2** under our optimized conditions in organic medium (conditions A) and led to the corresponding coupling adducts **3** in very good to excellent yields (Table 3, entries 1–3). Under our optimized conditions in hydro-organic medium (conditions B), however, only indole (**1a**) was efficiently converted in the desired product. Analysis of the crude mixture by GCMS showed that pyrrole (**1b**), under conditions B, led to unidentified side reactions, while carbazole (**1c**) was simply less reactive in these conditions due to solubility issues.

The first azole to be submitted to our coupling reaction, imidazole (**1d**), led to very poor yields of **3d** under both organic and hydro-organic conditions, even when heated at 55 °C (Table 3, entry 4). On the other hand, the coupling of benzimidazole (**1e**), pyrazole (**1f**) and indazole (**1g**) with vinyl diiodide **2** under our optimized conditions in organic medium (conditions A) led respectively to coupling products **3e**, **3f** and **3g** in good to very good yields (Table 3, entries 5–7). All azole derivatives (**1d-g**) coupled less efficiently with vinyl diiodide **2** under our optimized conditions in hydro-organic medium (conditions B), which again seem to be due to solubility issues.

We tried to rationalize the peculiarly low reactivity of imidazole (**1d**) by comparing the acidity of the tested azole derivatives and their reported nucleophilic behavior in a S_NAr reaction.[10] The absence of correlation between these parameters led us to solely attribute the low reactivity of imidazole (**1d**) to its poor solubility in both organic and hydro-organic media.

In order to establish the functional group tolerance and the substituents effect of our β-iodovinylation reaction, we looked at the reactivity of indole derivatives bearing substituents on positions 3 and 5, and compared them to unsubstituted indole **1a**. We coupled indole derivatives **5** with vinyl diiodide **2** under both our optimized conditions A and B. These results are reported in Table 4.

The presence of an electron-donating group in 5-methoxyindole (**5a**) surprisingly diminished the efficiency of the coupling reaction in both media compared to unsubstituted indole **1a** (73% vs 95% and 44% vs 94%), but still afforded the desired product **6a** in good yield under conditions A (Table 4, entry 1).

The coupling of 5-nitroindole (**5b**) with vinyl diiodide **2** under our optimized conditions in organic medium (conditions A) led to the corresponding coupling adduct **6b** in fair yield, while the same transformation in hydro-organic medium (conditions B) afforded **6b** in excellent yield (Table 4, entry 2).

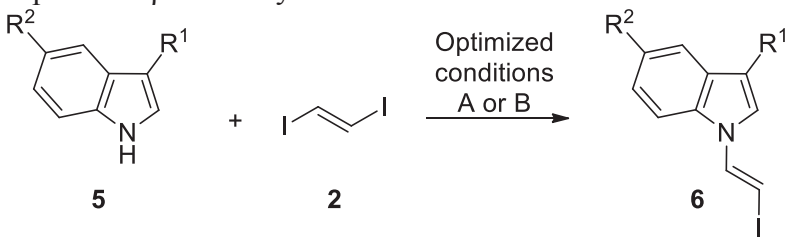
In this case, the presence of the nitro group seems to only have a detrimental effect on the reactivity of **5b** in organic medium because of solubility issues, which highlights the usefulness and the complementarity of our optimized conditions in hydro-organic medium.

The coupling reaction between 5-bromoindole (**5c**) and vinyl diiodide **2** led to similar yields under conditions A and B (73% and 79% respectively), but both yields are lower than with unsubstituted indole **1a** (95% and 94%) (Table 4, entry 3). We hypothesize this may be due to a deactivating effect of the bromo substituent leading to a slightly diminished nucleophilic character in **5c** versus **1a**. We ruled out the possibility of any side-reaction involving the aryl bromide moiety since analysis of the crude mixture by GCMS showed a clean albeit incomplete transformation.

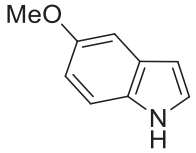
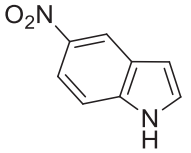
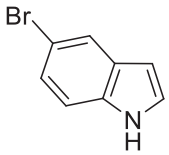
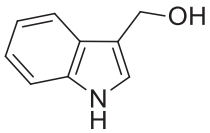
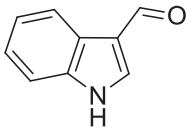
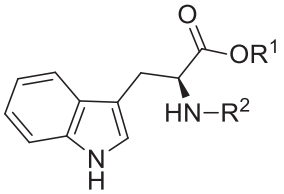
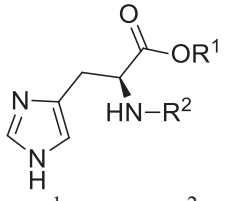
The coupling of 3-(hydroxymethyl)indole (**5d**) with vinyl diiodide **2** under our optimized conditions (either A or B) led to complete consumption of **5d** without any trace of the desired product **6d** (Table 4, entry 4). Analysis of the yellow crude mixture by GCMS showed that alcohol **5d** (off-white) was oxidized into aldehyde **5e** (yellow) under these conditions, probably leading to reduced and unreactive copper species. On the other hand, when subjected to the same conditions, aldehyde **5e** led to iodovinylated adduct **6e** in fair yield in both media (Table 4, entry 5).

We then extended our optimized β-iodovinylation conditions to aza-aromatic amino acids, tryptophan (**5f**) and histidine (**5h**) (Table 4, entries 6–7). When both unprotected amino acids were submitted to either conditions A or B, they were fully recovered without observing the corresponding products **6f** or **6h**. We hypothesize that these unprotected amino acids, under basic conditions, can act as inert ligand for the copper catalyst, thus forming highly stable and unreactive complexes. This is supported by the reactivity of their protected counterparts; protected tryptophan **5g** coupled smoothly with vinyl diiodide **2** under our optimized conditions in organic medium (conditions A) to form **6g** in good yield while protected histidine **5i** led to **6i** in poor yield under the same conditions (Table 4, entries 6–7). The reactivity of **5g** and **5i** follows the same trend as their free azole or pyrrole moiety: tryptophan (indole) >> histidine (imidazole) which opens the way to selective *N*-vinylation in peptides. Note that these protected amino acids **5g** and **5i** were unreactive under our optimized conditions in hydro-organic medium (conditions B) which may be due to hydrolysis of the methyl ester group (i.e. partial deprotection) in presence of aqueous potassium hydroxide. Also note that vinylation of **5g** and **5i** strictly occurred on the aza-aromatic ring and not on the carbamate moiety, which is consistent with our previous observations regarding the non-reactivity of acyclic *N*-alkylated carbamates under very similar conditions.[8b]

Table 4. Substrate scope in the β-iodovinylation of indole derivatives and aza-aromatic amino acids **5**



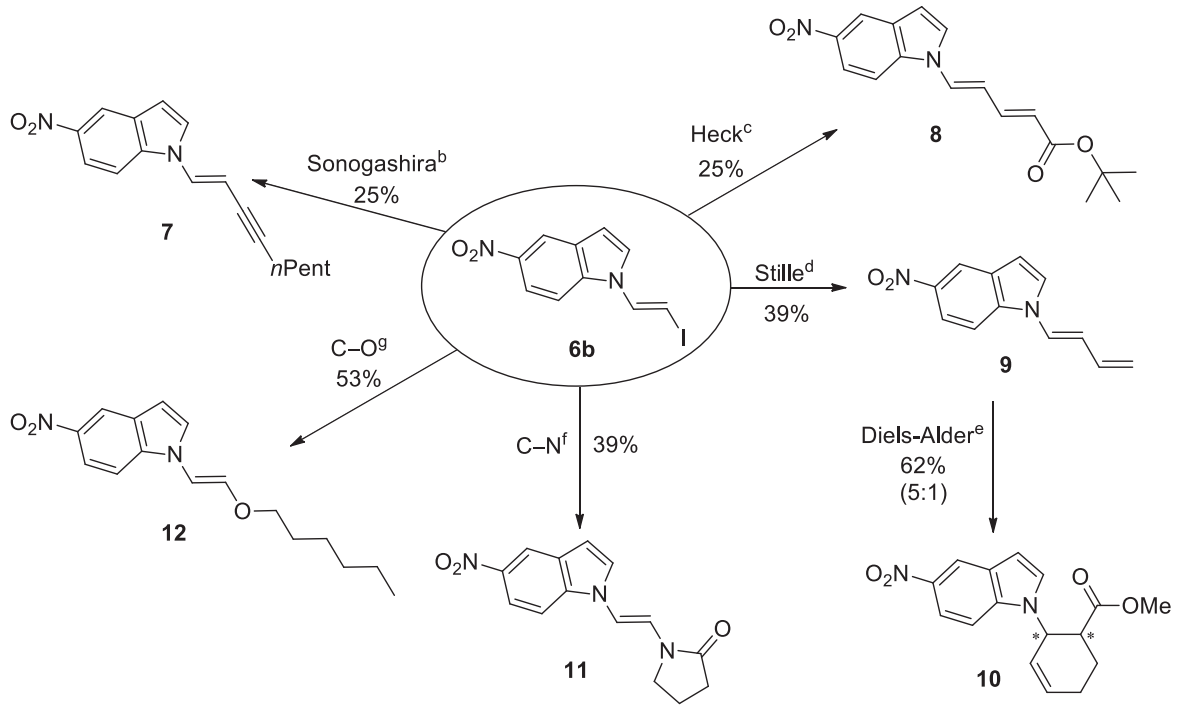
5 **2** **6**

Entry	Indole derivative **5**	Product **6**	Isolated yield Conditions A (organic)	Isolated yield Conditions B (hydro-organic)
1	 **5a**	**6a**	73%	49%
2	 **5b**	**6b**	55%	93%
3	 **5c**	**6c**	73%	79%
4	 **5d**	**6d**	0%	0%
5	 **5e**	**6e**	68%	53%
6	 **5f** (R^1=H and R^2=H) **5g** (R^1=Me and R^2=Boc)	**6f** **6g**	0% 70%	0% 0%
7	 **5h** (R^1=H and R^2=H) **5i** (R^1=Me and R^2=Boc)	**6h** **6i**	0% 20%	0% 1%

As previously mentioned, β-iodovinyl-azole and β-iodovinyl-pyrrole derivatives are potential key intermediates to access complex vinylated azole and pyrrole derivatives, but their reactivity in metal-catalyzed reactions remains undocumented. To investigate their reactivity, we used β-iodovinyl-5-nitroindole (**6b**) as a model substrate in a variety of transformations leading to C–C bond formation (Scheme 3). Note that this preliminary investigation aims to better understand the behavior of these peculiar substrates in various metal-catalyzed transformations, thus the yields in this section are yet to be optimized.

Compound **6b** was reacted with heptyne under Pasqua's conditions[11] to form the corresponding Sonogashira product, enyne **7**, in poor yield. When submitted to a Heck coupling reaction with *t*-butyl acrylate using conditions adapted from Okitsu's protocol,[12] model **6b** led solely to (*E,E*)-diene **8** although in poor yield. Stille cross-coupling between **6b** and tributyl(vinyl)tin under modified Mee's conditions[13] provided diene **9** in 39% yield. The latter was then converted into functionalized cyclohexene **10** in 62% yield via a Diels-Alder reaction with methyl acrylate using Smith's conditions.[14] For this transformation, we observed a complete regiocontrol along with a 5:1 *syn-anti* ratio.

We also used **6b** in couplings leading to the formation of C–heteroatom bonds (C–N and C–O). We coupled **6b** with 2-pyrrolidinone under the conditions we previously used to isolate bis-coupling adduct **4a** (see Scheme 2) and obtained bis-nitrogenated olefin **11** in 39% yield. To the best of our knowledge, the very few methods reported for the synthesis of analogs of **11** produce only *cis*[15] or symmetrical olefins,[16] thus defining our approach as a unique way to prepare this type of *trans* unsymmetrical bis-nitrogenated olefins. We further extended our functionalization of β-iodovinyl-5-nitroindole (**6b**) toward a C–O bond forming coupling reaction to access nitrogenated enol ether derivatives. In 2016 and 2018, we published the first examples of copper catalyzed coupling between β-iodovinyl-amide derivatives and allylic alcohols, a C–O bond forming reaction leading to β-(allyloxy)vinyl-amide derivatives in up to 90% yields.[7b,17] We exploited those conditions to couple model **6b** with hexanol at room temperature, leading to enol ether **12** in 53% yield. Only one other method is reported for the synthesis of nitrogenated enol ethers such as **12**, but the scope of this lengthy approach is limited to phenols and requires the use of strong bases (i.e. *n*BuLi and KH).[18] Note that all functionalization reactions performed to transform **6b** into compounds **7–12** proceeded with complete stereoretention of the starting (*E*)-olefin.



Scheme 3. Functionalization of β-iodovinyl-5-nitroindole (**6b**)[a]

[a]All reactions were performed on a 200 mg scale. All couplings (conditions b-d, f and g) were performed in nitrogen purged ace pressure tubes. Reported yields are for pure isolated products.
[b]Vinyl iodide **6b** (1 equiv), heptyne (2 equiv), $Pd(PPh_3)_4$ (5 mol%), CuI (20 mol%), *i*Pr_2NH-DMF (3:1) [0.5M], N_2, rt, 24 h.
[c]Vinyl iodide **6b** (1 equiv), *t*-butyl acrylate (3 equiv), $Pd(PPh_3)_4$ (5 mol%), Et_3N (3 equiv), MeCN [1M], N_2, 55 °C, 24 h.
[d]Vinyl iodide **6b** (1 equiv), tri-*n*-butyl(vinyl)tin (1.2 equiv), $Pd(PPh_3)_4$ (10 mol%), CuI (10 mol%), KF (2.4 equiv), DMF [0.5M], N_2, 55 °C, 24 h.
[e]Diene **9** (1 equiv), methyl acrylate (3 equiv), H_2O-MeOH (1:1) [0.05M], reflux, 10 h.
[f]Vinyl iodide **6b** (1 equiv), 2-pyrrolidinone (5 equiv), CuI (20 mol%), DMEDA (60 mol%), Cs_2CO_3 (3 equiv), 1,4-dioxane [1M], N_2, 100 °C, 24 h.
[g]Vinyl iodide **6b** (1 equiv), *n*-hexanol (2 equiv), CuI (30 mol%), DMEDA (45 mol%), Cs_2CO_3 (4 equiv), toluene [2M], N_2, rt, 30 h.

CONCLUSION

We developed conditions to enable the copper-catalyzed β-iodovinylation of azole and pyrrole derivatives in both organic and hydro-organic medium. Those two sets of conditions proved to be efficient and complementary to access β-iodovinylated azole and pyrrole derivatives in good to excellent yields with complete stereocontrol. Our method tolerates a variety of functional groups and can be applied to both electron-rich and electron-poor substrates. Further functionalization of the iodovinyl moiety of model **6b** using metal-catalyzed transformations demonstrated the wide potential of β-iodovinylated azole and pyrrole derivatives as key intermediates to access poly-substituted olefins, enynes, and dienes.

EXPERIMENTAL

General Information. All coupling reactions were nitrogen-purged and run in resealable pressure tubes (13 mm x 17.8 cm). All solvents were distilled prior to use. Ligands, azole derivatives and pyrrole derivatives were used without further purification. Thin-layer chromatographies (TLC) were carried out using 250 μm commercial silica gel plates containing F-254 indicator. Visualization was accomplished with UV light followed by dipping in phosphomolybdic acid (PMA) solution then heating. Purification of reactions was carried out by flash chromatography using silica gel 230–400 mesh (40–63 μm). During all optimization phases, yields were determined by GC-MS using 4-dimethylaminopyridine (DMAP) as standard and were recorded on an Agilent 6890N gas chromatograph coupled to an Agilent 5973 electron impact mass spectrometer. All compounds were fully characterized by spectroscopic analysis. The melting points were determined with an Electrothermal IA9100 melting point apparatus. IR spectra were recorded on pure samples with an FT-IR Thermo Scientific Nicolet is10 spectrometer. IR data are reported as follows: absorption peaks (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Varian 200 MHz NMR spectrometer using $CDCl_3$ (δ = 7.26 ppm), $(CD_3)_2CO$ (δ = 2.05 ppm) or $(CD_3)_2SO$ (δ = 2.50 ppm) as the reference. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using the same NMR apparatus at 50 MHz using $CDCl_3$ (δ = 77.16 ppm), $(CD_3)_2CO$ (δ = 29.84 and 206.26 ppm) or $(CD_3)_2SO$ (δ = 39.52 ppm) as the reference. NMR data are reported as follows: chemical shifts are reported in parts per million (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, qt = quintet, m = multiplet), number of protons, and coupling constants are reported in Hertz (Hz). HRMS data were collected on an Agilent 1200 series HPLC coupled with the 6210 Quadrupole Time-of-Flight (Q-TOF) MS detector, and using electrospray ionization (ESI). Copies of ^1H and ^{13}C NMR spectra of all new compounds are available free of charge via the Internet at https://www.heterocycles.jp/.

Procedure for the preparation of vinyl diiodide 2

Activated alumina (43 g, 0.42 mol, 3.5 equiv) was added to a 0.24M solution of iodine (30.6 g, 0.12 mol, 1.0 equiv) in hexanes (500 mL), and the purple solution was stirred at room temperature. An acetylene flow was applied to the stirring solution during 15 min, then the solution was stirred for 1 h. Another acetylene flow was applied to the stirring solution during 15 min, then the solution was stirred for 1 h. A last acetylene flow was applied to the stirring solution during 15 min, then the solution was stirred overnight. This three-flow process was done once a day for 3 consecutive days. The solution was filtered to remove the brown solid and the filtrate was concentrated under reduced pressure. The resulting pink solid was dissolved in hexanes, washed 3–5 times with $Na_2S_2O_4$ (10% aqueous solution), dried over

Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (hexanes) to give 18.6 g of vinyl diiodide **2** (60%).

(*E*)-1,2-Diiodoethene (2): white solid (60%); mp 71–72 °C; IR (neat, ν): 3056 (s), 1803 (w), 1594 (m), 1123 (s), 897 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.09 (s, 2H, =C(I)H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 80.1 (=C(I)H) ppm. Spectral data match the literature.[8a]

General procedures for the preparation of β-iodovinylated compounds (3 and 6): Conditions A – Organic medium

A mixture of azole **1** or indole derivative **5** (1.0 equiv), vinyl diiodide **2** (1.2 equiv), cesium carbonate (2.4 equiv), copper iodide (20 mol%), *N,N'*-dimethylethylenediamine (60 mol%), and 1,4-dioxane [1.0 M] was placed in an ace pressure tube. The vessel was capped, degassed with anhydrous nitrogen and stirred at 25 °C for 24 h. The reaction mixture was then diluted with DCM and filtered on Buchner. The filtrate was dried over magnesium sulfate and concentrated in vacuo. The crude products were purified by silica gel flash column chromatography (gradient eluent, 0–20% acetone in hexanes or 0–10% MeOH in $CHCl_3$) to afford the desired β-iodovinylated azole derivatives **3** and β-iodovinylated pyrrole derivatives **6**.

General procedures for the preparation of β-iodovinylated compounds (3 and 6): Conditions B – Hydro-organic medium

A mixture of azole or indole derivative **1** or **5** (1.0 equiv), vinyl diiodide **2** (1.2 equiv), potassium hydroxide (2.4 equiv), copper iodide (20 mol%), *N,N'*-dimethylethylenediamine (60 mol%), and THF:H_2O (1:10) [1.0M] was placed in an ace pressure tube. The vessel was capped, degassed with anhydrous nitrogen and stirred at 25 °C for 24 h. The reaction mixture was then diluted with DCM and filtered on Buchner. The filtrate was dried over magnesium sulfate and concentrated in vacuo. The crude products were purified by silica gel flash column chromatography (gradient eluent, 0–20% acetone in hexanes or 0–10% MeOH in $CHCl_3$) to afford the desired β-iodovinylated azole derivatives **3** and β-iodovinylated pyrrole derivatives **6**.

(*E*)-*N*-(2-Iodovinyl)indole (3a): yellow solid (95%, 486 mg); mp 105 °C (decomposition); IR (neat, ν) 3108, 3074 ,1617, 1519, 1455, 1318 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.13 (d, J = 13.7 Hz, 1H), 6.65 (d, J = 3.4 Hz, 1H), 7.06−7.38 (m, 3H), 7.47 (dd, J = 8.2 and 1.1 Hz, 1H), 7.62 (dd, J = 7.5 and 1.5 Hz, 1H), 7.71 (d, J = 13.7 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 57.4, 105.9, 109.5, 121.3, 121.4, 123.1, 123.2, 128.8, 134.5, 134.9. HRMS (ESI/TOF-Q) : Found *m/z* = 268.9703 $[M]^+$; Calcd for $C_{10}H_8IN$ = 268.9701.

(*E*)-*N*-(2-Iodovinyl)pyrrole (3b): pyrrole (**1b**) must be distilled prior to use; yellow solid (82%, 64 mg); mp 62 °C (decomposition); IR (neat, ν) 3112, 3062, 1617, 1522, 1480, 1288 cm^{-1}; ^1H NMR (200 MHz,

$CDCl_3$) δ 6.05 (d, *J* = 13.8 Hz, 1H). 6.22 (t, *J* = 2.2 Hz, 2H), 6.80 (t, *J* = 2.2 Hz, 2H), 7.31 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 58.0, 110.6 (2C), 118.5 (2C), 137.5. HRMS (ESI/TOF-Q): Found *m/z* = 219.9624 $[M+H]^+$; Calcd for C_6H_6IN + H = 219.9623.

(*E*)-*N*-(2-Iodovinyl)carbazole (3c): carbazole (**1c**) must be purified by recrystallization in benzene prior to use; white solid (81%, 78 mg); mp 105 °C (decomposition); IR (neat, ν) 3075, 3042, 1607, 1489, 1478, 1333, 1311 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.56 (d, *J* = 13.8 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.48 (td, *J* = 7.6 and 1.1 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 13.8 Hz, 1H), 8.06 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 63.9, 110.2 (2C), 120.4 (2C), 121.3 (2C), 123.9 (2C), 126.5 (2C), 134.2, 138.7 (2C). HRMS (ESI/TOF-Q): Found *m/z* = 319.9936 $[M+H]^+$; Calcd for $C_{14}H_{10}IN$ + H = 319.9931.

(*E*)-*N*-(2-Iodovinyl)imidazole (3d): light-brown solid (10%, 18 mg); mp 93−96 °C; IR (neat, ν) 3121−3056, 1666, 1625, 1492, 1235, 1175 cm^{-1}; ^1H NMR (200 MHz, $(CD_3)_2CO$) δ 6.79 (d, *J* = 14.1 Hz, 1H), 7.01 (s, 1H), 7.50 (s, 1H), 7.79 (d, *J* = 14.1 Hz, 1H), 7.84 (s, 1H); ^{13}C NMR (200 MHz, $(CD_3)_2CO$) δ 62.8, 115.7, 130.1, 134.3, 136.1. HRMS (ESI/TOF-Q): Found *m/z* = 220.9567 $[M+H]^+$; Calcd for $C_5H_5IN_2$ + H = 220.9576.

(*E*)-*N*-(2-Iodovinyl)benzimidazole (3e): white solid (73%, 84 mg); mp 102−103 °C; IR (neat, ν) 3121, 3064, 1636, 1490, 1457, 1281 cm^{-1}; ^1H NMR (200 MHz, $(CD_3)_2CO$) δ 6.60 (d, *J* = 13.9 Hz, 1H), 7.28-7.39 (m, 2H), 7.43−7.54 (m, 1H), 7.61 (d, *J* = 13.9 Hz, 1H), 7.76−7.85 (m, 1H), 8.02 (s, 1H); ^{13}C NMR (200 MHz, $(CD_3)_2CO$) δ 65.2, 110.2, 120.9,123.5, 124.3, 131.8, 132.5,140.1, 143.7. HRMS (ESI/TOF-Q): Found *m/z* = 270.9727 $[M+H]^+$; Calcd for $C_9H_7IN_2$ + H = 270.9732.

(*E*)-*N*-(2-Iodovinyl)pyrazole (3f): yellow oil (75%, 145 mg); IR (neat, ν) 3140−3077, 1631, 1520, 1387, 1310, 1203 cm^{-1}; ^1H NMR (200 MHz, $(CD_3)_2CO$) δ 6.38 (dd, *J* = 2.3 and 2.0 Hz, 1H), 6.76 (d, *J* = 13.7 Hz, 1H), 7.62 (d, *J* = 1.2 Hz, 1H), 7.78 (d, *J* = 13.7 Hz, 1H), 7.88 (d, *J* = 2,7 Hz, 1H); ^{13}C NMR (200 MHz, $(CD_3)_2CO$) δ 61.7, 106.9, 128.7, 137.3, 141.3. HRMS (ESI/TOF-Q): Found *m/z* = 220.9565 $[M+H]^+$; Calcd for $C_5H_5IN_2$ + H = 220.9576.

(*E*)-*N*-(2-Iodovinyl)indazole (3g): light-yellow solid (84%, 195 mg); mp 105−107 °C; IR (neat, ν) 3108−3042, 1638, 1614, 1464, 1413, 1318, 1159 cm^{-1}; ^1H NMR (200 MHz, $(CD_3)_2CO$) δ 6.71 (d, *J* = 13.3 Hz, 1H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 8,2 Hz, 2H) 8.12 (d, *J* = 13.3 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (200 MHz, $(CD_3)_2CO$) δ 58.9, 109.4, 121.3, 122.2, 124.5, 127.7, 134.3, 136.8, 138.2. HRMS (ESI/TOF-Q): Found *m/z* = 270.9720 $[M+H]^+$; Calcd for $C_9H_7IN_2$ + H = 270.9732.

(*E*)-*N*-(2-Iodovinyl)-5-methoxyindole (6a): light-yellow solid (73%, 54 mg); mp 83 °C (decomposition); IR (neat, ν) 3109, 3067, 2922, 1610, 1472, 1448, 1247 cm^{-1}; ^1H NMR (200 MHz,

$(CD_3)_2CO$) δ 3.81 (s, 3H), 6.45 (d, *J* = 13.7 Hz, 1H), 6.59 (d, *J* = 3.5 Hz, 1H), 6.89 (dd, *J* = 9.0 and 2.5 Hz, 1H), 7.10 (d, *J* = 2.5 Hz, 1H), 7.69−7.58 (m, 2H), 7.91 (d, *J* = 13.7 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 55.8, 56.8, 103.2, 105.5, 110.3, 112.9, 123.9, 129.4, 129.9, 134.7, 155.2. HRMS (ESI/TOF-Q): Found *m/z* = 299.9873 $[M+H]^+$; Calcd for $C_{11}H_{10}INO$ + H = 299.9885.

(*E*)-*N*-(2-Iodovinyl)-5-nitroindole (6b): yellow solid (93%, 71 mg); mp 118−120 °C; IR (neat, ν) 3100, 3068, 1617, 1505, 1448, 1328, 1308 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.39 (d, *J* = 13.7 Hz, 1H), 6.82 (d, *J* = 3.4 Hz, 1H), 7.41−7.57 (m, 2H), 7.72 (d, *J* = 13.8 Hz, 1H), 8.19 (dd, *J* = 9.1 and 2.3 Hz, 1H), 8.57 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 61.9, 107.5, 109.5, 118.3, 118.7,126.4, 128.1, 133.6, 137.3, 142.8. HRMS (ESI/TOF-Q): Found *m/z* = 314.9613 $[M+H]^+$; Calcd for $C_{10}H_7IN_2O_2$ + H = 314.9630.

(*E*)-*N*-(2-Iodovinyl)-5-bromoindole (6c): beige solid (79%, 70 mg); mp 67−70 °C; IR (neat, ν) 3107, 3071, 1615, 1524, 1452, 1306, 1277 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.15 (d, *J* = 13.7 Hz, 1H), 6.56 (t, *J* = 3.4 Hz, 1H), 7.42−7.20 (m, 3H), 7.61 (d, *J* = 13.8 Hz, 1H), 7.72 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 58.7, 105.2, 110.8, 114.5, 123.8, 124.4, 125.9, 130.4, 133.5, 134.1. HRMS (ESI/TOF-Q): Found *m/z* = 347.8889 $[M+H]^+$; Calcd for $C_{10}H_7BrIN$ + H = 347.8885.

(*E*)-*N*-(2-Iodovinyl)-3-formylindole (6e): off-white solid (68%, 174 mg); mp 122−123 °C; IR (neat, ν) 3109−3045, 2854−2753, 1652, 1615, 1532, 1458, 1401, 1368, 1191 cm^{-1}; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 6.99 (d, *J* = 13.7 Hz, 1H), 7.29−7.44 (m, 2H), 7.82 (d, *J* = 7.0 Hz, 1H), 8.05 (d, *J* = 14.1 Hz, 1H), 8.23 (dd, *J* = 6.6 and 2.0, 1H), 8.45 (s, 1H), 10.06 (s, 1H); ^{13}C NMR (200 MHz, $(CD_3)_2CO$) δ 64.3, 110.7, 120.4, 121.7, 123.5, 124.8, 124.9, 133.8, 134.8, 136.2, 184.7. HRMS (ESI/TOF-Q): Found *m/z* = 297.9716 $[M+H]^+$; Calcd for $C_{11}H_8INO$ + H = 297.9729.

(*E*)- *N*-(*tert*-Butoxycarbonyl)-*N'*-(2-iodovinyl)-L-tryptophan methyl ester (6g): beige solid (70%, 247 mg); mp 120−122 °C; IR (neat, ν) 3364, 3083−3053, 2988−2853, 1731, 1678, 1617, 1516, 1459, 1367, 1248, 1162 cm^{-1}; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 1.36 (s, 9H), 3.17 (dd, *J* = 14.6 and 7.6 Hz, 1H), 3.29 (dd, *J* = 14.6 and 5.7 Hz, 1H), 3.66 (s, 3H), 4.50 (dd, *J* = 6.8 and 5.9 Hz, 1H), 6.18 (d, *J* = 7.8 Hz, 1H), 6.41 (d, *J* = 13.7 Hz, 1H), 7.13−7.31 (m, 2H), 7.55 (s, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (200 MHz, $(CD_3)_2CO$) δ 27.6, 29.2, 51.4, 54.1, 56.2, 78.5, 109.9, 114.9, 119.0, 120.9, 122.1, 123.2, 128.6, 134.2, 135.3, 155.3, 172.3. HRMS (ESI/TOF-Q): Found *m/z* = 493.0586 $[M+Na]^+$; Calcd for $C_{19}H_{23}IN_2O_4$ + Na = 493.0600.

(*E*)- *N*-(*tert*-Butoxycarbonyl)-*N'*-(2-iodovinyl)-L-histidine methyl ester (6i): colorless oil (20%, 61 mg); IR (neat, ν) 3359, 3144−3071, 2977−2930, 1741, 1698, 1490, 1365, 1162 cm^{-1}; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 1.39 (s, 9H), 2.96−3.00 (m, 2H), 3.63 (s, 3H), 4.40−4.50 (m, 1H), 6.42 (d, *J* = 8.2 Hz, 1H),

6.72 (d, *J* = 13.7 Hz, 1H), 7.30 (s, 1H), 7.72 (d, *J* = 13.7 Hz, 1H), 7.77 (s, 1H); ^{13}C NMR (200 MHz, $(CD_3)_2CO$) δ 27.7, 29.2, 51.3, 53.6, 62.6, 78.4, 113.2, 134.1, 136.1, 139.1, 155.3, 172.0. HRMS (ESI/TOF-Q): Found *m/z* = 422.0553 $[M+H]^+$; Calcd for $C_{14}H_{20}IN_3O_4$ + H = 422.0577.

Procedure for the preparation of diadduct 4a

A mixture of indole **1a** (446 mg, 3.81 mmol, 2.5 equiv), vinyl diiodide **2** (424 mg, 1.51 mmol, 1.0 equiv), cesium carbonate (1484 mg, 4.56 mmol, 3 equiv), copper iodide (58 mg, 0.31 mmol, 20 mol%), *N,N'*-dimethylethylenediamine (100 μL, 0.93 mmol, 60 mol%), and 1,4-dioxane [1.0M] was placed in an ace pressure tube. The vessel was capped, degassed with anhydrous nitrogen and stirred at 90 °C for 24 h. The reaction mixture was then cooled to room temperature. The reaction mixture was then diluted with DCM and filtered on Buchner. The filtrate was dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (gradient eluent, 0−5% acetone in hexanes) and afforded 283 mg of diadduct **4a** (72%).

(*E*)-1,2-Bis(*N*-indolyl)ethene (4a): off-white solid (72%, 283 mg); mp 171−173 °C; IR (neat, ν) 3398, 3137−3046, 2961−2920, 1516, 1455, 1320, 1224, 1197, 1116 cm^{-1}; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) [Note: at this temperature, two rotamers (A and B) are visible in a 2:1 ratio, due to restricted rotation of the molecule] δ 6.46 [B](dd, *J* = 2.1 and 2.1 Hz, 0.66H), 6.70 [A](d, *J* = 3.5 Hz, 1.34H), 6.96−7.06 (m, 2H), 7.13 [A](t, *J* = 7.4 Hz, 1.34H), 7.22−7.33 (m, 2H), 7.42 [B](d, *J* = 7.8 Hz, 0.66H), 7.57 [B](d, *J* = 7.8 Hz, 0.66H), 7.64 [A](d, *J* = 5.4 Hz, 1.34H), 7.77 [B](d, *J* = 8.6 Hz, 0.66H), 7.84 [A](d, *J* = 3.1 Hz, 1.34H), 7.93 (s, 2H); ^{13}C NMR (200 MHz, $(CD_3)_2CO$) δ 101.4 and 104.2 [B+A], 110.0 and 111.2 [A+B], 115.0, 119.0 and 120.1 [A+B], 120.4 and 120.9 [A+B], 121.1 and 122.3 [B+A], 124.6 and 124.9 [B+A], 129.1, 136.0. HRMS (ESI/TOF-Q): Found *m/z* = 259.1225 $[M+H]^+$; Calcd for $C_{18}H_{14}N_2$ + H = 259.1235.

Procedure for the preparation of enyne 7

Heptyne (185 μL, 1.42 mmol, 2 equiv), $Pd(PPh_3)_4$ (42 mg, 0.036 mmol, 5 mol%) and copper(I) iodide (28 mg, 0.145 mmol, 20 mol%) were added to a 0.5M solution of vinyl iodide **6b** (222 mg, 0.71 mmol, 1 equiv) in $(i\text{-Pr})_2$NH:DMF (3:1) (700 μL) in an ace pressure tube. The vessel was degassed with anhydrous nitrogen, capped, and stirred at 25 °C for 24 h. Et_2O and water were added to the solution, and the organic layer was washed with HCl (1M aqueous solution), then with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (gradient eluent, 0−2% acetone in hexanes) and afforded 49 mg of desired enyne **7** (25%).

(*E*)-*N*-(2-(Hept-1-ynyl)vinyl)-5-nitroindole (7): yellow oil (25%, 49 mg); IR (neat, ν) 3142−3029, 2954−2858, 1637, 1514, 1469, 1450, 1334, 1312, 1070 cm^{-1}; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) [Note: at this temperature, two rotamers (A and B) are visible in a 3:1 ratio, due to restricted rotation of the

molecule] δ 0.90 (t, *J* = 6.8 Hz, 3H), 1.26−1.64 (m, 6H), 2.37 [A](td, *J* = 7.0 and 2.2 Hz, 1.5H), 2.46 [B](td, *J* = 7.0 and 2.5 Hz, 0.5H), 5.46 [B](dt, *J* = 9.4 and 2.3 Hz, 0.25H), 6.13 [A](dt, *J* = 14.5 and 2.3 Hz, 0.75H), 6.94 (d, *J* = 3.5 Hz, 1H), 7.43 [B](d, *J* = 9.4 Hz, 0.25H), 7.70 [A](d, *J* = 14.5 Hz, 0.75H), 7.90−7.93 (m, 2H), 8.13 (dd, *J* = 9.4 and 2.2 Hz, 1H), 8.56 [A](d, *J* = 2.3 Hz, 0.75H), 8.67 [B](d, *J* = 3.5 Hz, 0.25H); ^{13}C NMR (200 MHz, $(CD_3)_2CO$) δ 13.4, 19.1 and 19.2 [A+B], 21.97 and 22.00 [B+A], 28.0 and 28.4 [B+A], 30.9 and 31.0 [A+B], 76.4 and 76.6 [B+A], 92.3 and 94.9 [A+B], 96.8 and 98.1 [A+B], 106.2 and 107.5 [B+A], 110.4, 117.4 and 117.6 [B+A], 117.7 and 117.9 [B+A], 127.0 and 127.8 [A+B], 128.6 and 128.7 [B+A], 132.0, 138.0 and 138.6 [A+B], 142.6 and 142.8 [A+B]. HRMS (ESI/TOF-Q): Found *m/z* = 283.1434 $[M+H]^+$; Calcd for $C_{17}H_{18}N_2O_2$ + H = 283.1447.

Procedure for the preparation of diene 8

t-Butyl acrylate (150 μL, 1.03 mmol, 3 equiv), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol, 5 mol%) and triethylamine (140 μL, 1.00 mmol, 3 equiv) were added to a 1M solution of vinyl iodide **6b** (106 mg, 0.34 mmol, 1 equiv) in MeCN (340 μL) in an ace pressure tube. The vessel was degassed with anhydrous nitrogen, capped, and stirred at 25 °C for 24 h. Et_2O and water were added to the solution, and the organic layer was washed with HCl (1M aqueous solution), then with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (gradient eluent, 0−5% acetone in hexane) and afforded 26 mg of desired diene **8** (25%).

(*E,E*)-*N*-(5-(*tert*-Butoxy)-5-oxopenta-1,3-dienyl))-5-nitroindole (8): yellow-orange solid (25%, 26 mg); mp 175−176 °C; IR (neat, ν) 3127−3076, 2971−2874, 1700, 1635, 1510, 1461, 1370, 1331, 1287, 1251, 1125 cm^{-1}; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 1.49 (s, 9H), 5.94 (d, *J* = 15.2 Hz, 1H), 6.87 (dd, *J* = 13.7 and 11.2 Hz), 7.01 (d, *J* = 3.5 Hz, 1H), 7.45 (dd, *J* = 15.0 and 11.1 Hz, 1H), 7.92−8.07 (m, 3H), 8.17 (dd, *J* = 9.0 and 2.3 Hz, 1H), 8.58 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (200 MHz, $(CD_3)_2CO$) δ 27.5, 79.4, 108.3, 110.5, 113.4, 117.7, 118.2, 121.8, 127.1, 128.9, 131.6, 138.5, 141.5, 142.9, 165.6. HRMS (ESI/TOF-Q): Found *m/z* = 337.1153 $[M+Na]^+$; Calcd for $C_{17}H_{19}N_2O_4$ + Na = 337.1164.

Procedure for the preparation of diene 9

Tributyl(vinyl)tin (260 μL, 0.89 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (85 mg, 0.073 mmol, 10 mol%), copper(I) iodide (15 mg, 0.077 mmol, 10 mol%) and potassium fluoride (104 mg, 1.79 mmol, 2.4 equiv) were added to a 0.5M solution of vinyl iodide **6b** (229 mg, 0.73 mmol, 1 equiv) in DMF (1.5 mL) in an ace pressure tube. The vessel was degassed with anhydrous nitrogen, capped, and heated in an oil bath at 55 °C for 24 h. The reaction mixture was then cooled to room temperature. Et_2O and water were added to the solution, and the resulting mixture was washed with KF (10% aqueous solution), then with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel

flash column chromatography. The purification was performed using a gradient eluent (0−2% acetone in hexanes) and afforded 61 mg of desired diene **9** (39%).

(*E*)-*N*-(Buta-1,3-dienyl)-5-nitroindole (9): yellow solid (39%, 61 mg); mp 103−104 °C; IR (neat, ν) 3134−3034, 2981−2853, 1646, 1506, 1450, 1324, 1285, 1227 cm^{-1}; ^1H NMR (200 MHz, $(CD_3)_2CO$) δ 5.14 (dd, *J* = 9.8 and 2.0 Hz, 1H), 5.33 (dd, *J* = 16.2 and 2.1 Hz, 1H), 6.49−6.78 (m, 2H), 6.92 (d, *J* = 3.5 Hz, 1H), 7.59 (d, *J* = 13.3 Hz, 1H), 7.78 (d, *J* = 9.4 Hz, 1H), 7.93 (d, *J* = 3.5 Hz, 1H), 8.10 (dd, *J* = 9.2 and 2.1 Hz, 1H), 8.54 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (200 MHz, $(CD_3)_2CO$) δ 107.0, 110.1, 116.2, 117.4, 117.6, 117.7, 126.0, 127.3, 128.5, 134.3, 138.1, 142.4. HRMS (ESI/TOF-Q): Found *m/z* = 215.0811 $[M+H]^+$; Calcd for $C_{12}H_{10}N_2O_2$ + H = 215.0821.

Procedure for the preparation of cyclohexene 10

In a 10 mL round bottom flask connected to a condenser, methyl acrylate (230 μL, 2.54 mmol, 10 equiv) was added to a 0.1M solution of diene **9** (52 mg, 0.24 mmol, 1 equiv) in a 1:1 water-MeOH cosolvent (2.5 mL), and the yellow solution was refluxed for 10 h. The reaction mixture was then cooled to room temperature. Et_2O and water were added to the solution, and the resulting mixture was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography. The purification was performed using a gradient eluent (0−40% Et_2O in hexanes) which afforded 38 mg of *syn*-**10** along with 8 mg of *anti*-**10** for a total of 46 mg of cyclohexene **10** (62%) and a 5:1 *syn*-*anti* ratio.

***syn*-*N*-(6-(Methoxycarbonyl)cyclohex-2-en-1-yl)-5-nitroindole (*syn*-10):** yellow oil (51%, 38 mg); IR (neat, ν) 3101−3029, 2949−2838, 1738, 1509, 1333, 1312, 1193, 1070 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.91−2.03 (m, 2H), 2.07−2.51 (m, 2H), 3.00−3.11 (m, 1H), 3.17 (s, 3H), 5.44 (dd, *J* = 4.9 and 4.9 Hz, 1H), 5.83 (ddd, *J* = 9.8, 4.5 and 2.5 Hz, 1H), 6.25 (ddd, *J* = 9.8, 4.9 and 2.0 Hz, 1H), 6.66 (d, *J* = 3.1 Hz, 1H), 7.37 (d, *J* = 3.5 Hz, 1H), 7.46 (d, *J* = 9.0 Hz, 1H), 8.08 (dd, *J* = 9.2 and 2.1 Hz, 1H), 8.54 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 19.5, 24.1, 44.9, 50.7, 51.6, 104.3, 109.7, 116.8, 118.1, 123.8, 127.9, 130.2, 133.3, 139.0, 141.6, 172.2. HRMS (ESI/TOF-Q): Found *m/z* = 301.1187 $[M+H]^+$; Calcd for $C_{16}H_{16}N_2O_4$ + H = 301.1188.

***anti*-*N*-(6-(Methoxycarbonyl)cyclohex-2-en-1-yl)-5-nitroindole (*anti*-10):** yellow oil (11%, 8 mg); IR (neat, ν) 3103−3033, 2948−2839, 1732, 1511, 1332, 1308, 1204, 1169, 1068 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.01−2.10 (m, 2H), 2.27−2.35 (m, 2H), 2.95 (td, *J* = 9.3 and 4.6 Hz, 1H), 3.50 (s, 3H), 5.42 (ddd, *J* = 11.3, 5.1 and 2.7 Hz, 1H), 5.73 (ddd, *J* = 10.0, 4.7 and 2.1 Hz, 1H), 6.13 (ddd, *J* = 10.0, 6.4 and 3.7 Hz, 1H), 6.67 (d, *J* = 3.5 Hz, 1H), 7.29 (d, *J* = 3.5 Hz, 1H), 7.47 (d, *J* = 9.4 Hz, 1H), 8.09 (dd, *J* = 9.0 and 2.3 Hz, 1H), 8.56 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 23.8, 24.7, 46.2, 52.1, 54.7,

104.4, 110.1, 117.1, 118.2, 125.8, 128.1, 129.5, 131.5, 138.4, 141.6, 173.9. HRMS (ESI/TOF-Q): Found *m/z* = 301.1171 $[M+H]^+$; Calcd for $C_{16}H_{16}N_2O_4$ + H = 301.1188.

Procedure for the preparation of bis-nitrogenated olefin 11

2-Pyrrolidinone (292 mg, 3.43 mmol, 5 equiv), cesium carbonate (673 mg, 2.07 mmol, 3 equiv), copper(I) iodide (27 mg, 0.14 mmol, 20 mol%) and *N,N′*-dimethylethylenediamine (45 μL, 0.42 mmol, 60 mol%) were added to a 1M solution of vinyl iodide **6b** (215 mg, 0.69 mmol, 1 equiv) in 1,4-dioxane in an ace pressure tube. The vessel was degassed with anhydrous nitrogen, capped, and heated in an oil bath at 100 °C for 24 h. The reaction mixture was then cooled to room temperature, diluted with DCM, filtered with a Buchner funnel, and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography. The purification was performed using a gradient eluent (0−30% acetone in hexanes) and afforded 72 mg of desired bis-nitrogenated olefin **11** (39%).

(*E*)-*N*-(2-(2-Oxopyrrolidinyl)vinyl)-5-nitroindole (11): yellow-orange solid (39%, 72 mg); mp 221−223 °C; IR (neat, ν) 3112−3035, 2981−2824, 1682, 1506, 1416, 1402, 1318, 1283, 1248, 1224, 1066 cm^{-1}; ^1H NMR (200 MHz, $(CD_3)_2SO$) δ 2.10 (qt, *J* = 7.3 Hz, 2H), 2.43 (t, *J* = 8.2 Hz, 2H), 3.67 (t, *J* = 7.0 Hz, 2H), 6.89 (d, *J* = 3.5 Hz, 1H), 7.18 (d, *J* = 12.9 Hz, 1H), 7.50 (d, *J* = 13.3 Hz, 1H), 7.89 (d, *J* = 9.4 Hz, 1H), 8.08 (d, *J* = 9.4, 2H), 8.57 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (200 MHz, $(CD_3)_2SO$) δ 17.6, 30.9, 45.8, 106.6, 110.8, 111.3, 117.59, 117.62, 118.2, 128.1, 129.6, 138.5, 141.8, 173.4. HRMS (ESI/TOF-Q): Found *m/z* = 272.1024 $[M+H]^+$; Calcd for $C_{14}H_{13}N_3O_3$ + H = 272.1035.

Procedure for the preparation of enol ether 12

Hexanol (91 μL, 0.73 mmol, 2 equiv), cesium carbonate (474 mg, 1.45 mmol, 4 equiv), copper(I) iodide (25 mg, 0.13 mmol, 30 mol%) and *N,N′*-dimethylethylenediamine (18 μL, 0.16 mmol, 45 mol%) were added to a 2M solution of vinyl iodide **6b** (114 mg, 0.36 mmol, 1 equiv) in toluene in an ace pressure tube. The vessel was degassed with anhydrous nitrogen, capped, and stirred at 25 °C for 24 h. The reaction mixture was then diluted with DCM, filtered with a Buchner funnel, and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography. The purification was performed using a gradient eluent (0−20% acetone in hexanes) and afforded 42 mg of desired enol ether **12** (53%).

(*E*)-*N*-(2-(Hexyloxy)vinyl)-5-nitroindole (12): yellow-brown oil (53%, 42 mg); IR (neat, ν) 3136−3018, 2950−2858, 1610, 1509, 1331, 1307, 1214, 1181, 1068 cm^{-1}; ^1H NMR (200 MHz, $(CD_3)_2CO$) δ 0.90 (t, *J* = 6.4 Hz, 3H), 1.26−1.52 (m, 6H), 1.74 (qt, *J* = 6.7 Hz, 2H), 3.94 (t, *J* = 6.6 Hz, 2H), 6.79−6.86 (m, 2H), 7.20 (d, *J* = 11.3 Hz, 1H), 7.55−7.64 (m, 2H), 8.06 (dd, *J* = 9.0 and 2.3 Hz, 1H), 8.55 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (200 MHz, $(CD_3)_2CO$) δ 13.4, 22.4, 25.4, 29.1, 31.4, 70.6, 104.6, 105.7, 110.2, 116.9, 117.5, 127.9, 130.9, 139.0, 141.7, 146.5. HRMS (ESI/TOF-Q): Found *m/z* = 289.1538 $[M+H]^+$; Calcd for $C_{16}H_{20}N_2O_3$ + H = 289.1552.

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