Titanium-Catalyzed Hydrohydrazination with Monosubstituted Hydrazines: Catalyst Design, Synthesis, and Reactivity

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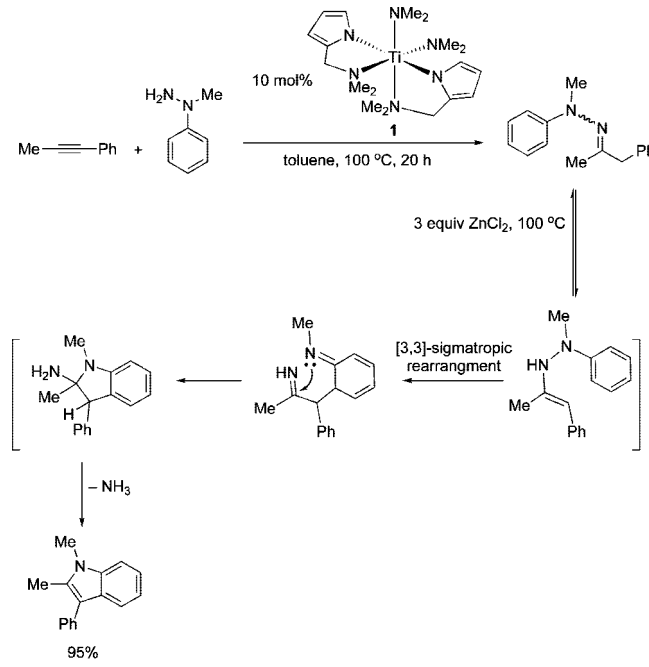
A new titanium catalyst using an ethylene diamine backbone with pyrrolyl-α-methyl groups on the diamine nitrogens has been developed for the hydrohydrazination of alkynes with monosubstituted hydrazines. The catalyst cleanly hydrohydrazinates terminal and internal alkynes with monosubstituted hydrazines bearing both alkyl and aryl substituents. One-pot Fischer indole cyclization led to *NH*-indoles in moderate to good yield. For example, 2-methyltryptamine was synthesized directly from 5-chloropent-1-yne with phenylhydrazine by hydrohydrazination and Fischer indole cyclization in a one-pot procedure. A variety of heterocycles, including pyrazoles and various hydropyridazines, can be generated using titanium-catalyzed hydrohydrazination. One of the products, 1,2-bis(2-methyl-3-indolyl)ethane, was structurally characterized.

Introduction

New methodologies for formation of C−N bonds by addition of *NH*-containing compounds across C−C unsaturated bonds has been of continuing interest for many years as an atom-efficient synthesis of nitrogen compounds. These reactions allow access to heterocyclic structures that act as the core of many natural products and pharmaceuticals.[1] Hydroamination, addition of H_2NR, for example, across a C−C unsaturation can be catalyzed by a host of metal complexes.[2] The first example of hydrohydrazination, formal addition of hydrazine across double or triple bonds, was the titanium-catalyzed addition of 1,1-disubsituted hydrazines to alkynes reported in 2002.[3,4] In these reactions, hydrazones were generated, and, if aryl-substituted hydrazines were used, Fischer indole cyclization resulted in isolation of the corresponding *N*-substituted indoles.

For titanium hydrohydrazination, only reactions involving 1,1-disubstituted hydrazines have been reported thus far with no examples of monosubstituted hydrazine reactions appearing in the literature. For 1,1-disubstituted hydrazine substrates, pyrrole-based ligand frameworks on titanium were effective (Scheme 1). Our originally reported design was $Ti(dap)_2(NMe_2)_2$ (**1**), where dap = 2-(dimethylaminomethyl)pyrrole. Also in the original report was a quite reactive thiolate-based catalyst, $Ti(SC_6F_5)_2(NMe_2)_2(NHMe_2)$. More recently, Beller and co-workers used a Cp-based titanium catalyst for a similar transformation.[5] In addition, they reported alkoxide-based ligands on titanium for hydrohydrazination with 5-chloropent-1-yne to generate *N*-substituted tryptamines.[6] In 2005, the same

Scheme 1. Hydrohydrazination with 1,1-Disubstituted Hydrazines and Formation of *N*-Substituted Indoles



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10.1021/om700852v CCC: $40.75
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group presented a similar transformation generating different *N*-substituted tryptophol derivatives.[7]

Since the discovery of the Fischer indole synthesis in 1883, synthesis and functionalization of indoles has remained an active area of research. A variety of modern and well-documented methods are available.[8] For example, Pd-catalyzed coupling and annulation reactions have been employed in synthesis of indole frameworks.[9] Recently, titanium-based hydroamination of alkynes followed by Heck couplings have been developed by Ackermann for the synthesis of *NH*-indoles.[10]

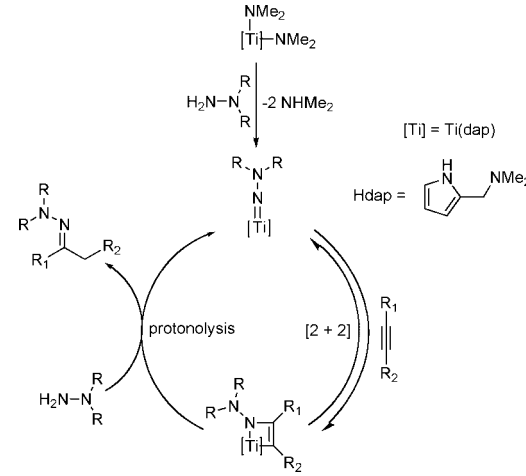
Titanium-catalyzed hydrohydrazination of alkynes with 1,1-disubstituted hydrazines results in the synthesis of *N*-substituted indoles from aryl-bearing hydrazones in the presence of an external Lewis acid, $ZnCl_2$ (Scheme 1). However, indole-containing natural products and pharmaceuticals more often contain *NH*-indoles.[11] Herein, we report the first catalyst active for hydrohydrazination with monosubstituted hydrazines, synthesis of *NH*-hydrazones, and in situ synthesis of a variety of heterocycles using these substrates.

Results and Discussion

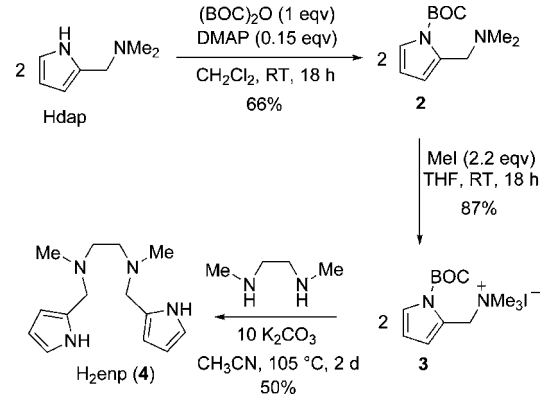
In titanium-catalyzed hydrohydrazination, the reactions are believed to follow a pathway similar to that discovered for hydroamination by Bergman and co-workers using zirconocene as catalyst (Scheme 2).[12] In the first step, a titanium hydrazido(2−) complex is generated from the bis(dimethylamido) precatalyst with the loss of 2 equiv of dimethylamine.[13] The hydrazido(2−) then undergoes a [2+2]-cycloaddition reaction with an alkyne, forming an azatitanacyclobutene intermediate. Finally, the metallacycle undergoes protonolysis with hydrazine to form product and regenerate the metal–ligand multiple bond.

In an attempt to extend the hydrohydrazination reaction to monosubstituted hydrazines, we investigated the reaction between 1-hexyne and phenylhydrazine with our previous catalysts $Ti(dap)_2(NMe_2)_2$ (**1**) and $Ti(SC_6F_5)_2(NMe_2)_2(NHMe_2)$ at 100 °C for 16 h. Both of the catalysts did not result in any hydrohydrazination product. In addition, we did not observe any hydrazone product with $Ti(NMe_2)_4$, where all the ligands are protolytically labile. Reaction of **1** with 10 equiv of phenylhydrazine resulted in greater than 1 equiv of Hdap being generated per titanium. Consequently, the dap ancillaries may be too protolytically labile to support monosubstituted hydrazine reactivity.

Scheme 2. Proposed Mechanistic Pathway for the Hydrohydrazination Reaction Using 1,1-Disubstituted Hydrazines



Scheme 3. Synthesis of H_2enp



Therefore, we attempted to increase the protolytic stability of the ancillary ligand set by using a tetradentate ligand instead of two bidentate ligands. For the synthesis of the new tetradentate ligand (Scheme 3), Hdap[14] was converted to *N*-(BOC)-dap (**2**) with $(BOC)_2O$ and DMAP. The tertiary amine of the BOC-protected dap was quarternized with methyl iodide to form the ammonium salt (**3**). Reaction of **3** with *N*,*N*′-dimethyl-1,2-ethylenediamine in the presence of excess K_2CO_3 formed the desired ligand H_2enp (**4**) in ∼50% yield with concomitant pyrrole nitrogen deprotection.

Next the new titanium precatalyst $Ti(enp)(NMe_2)_2$ (**5**) was prepared by reaction of 1 equiv of H_2enp with $Ti(NMe_2)_4$ as shown in Figure 1. The expected structure has two pyrroles coordinating in an η^1-fashion with two dimethylamido fragments mutally *cis*, which is consistent with the spectroscopic properties of the molecule.[15]

In order to probe the substrate scope of $Ti(enp)(NMe_2)_2$ (**5**), both terminal and internal alkynes were treated with different monosubstituted hydrazines in the presence of catalytic **5**. Test

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(15) The zirconium derivative has the geometry described in a structure determined by X-ray diffraction and is spectroscopically similar. Barnea, E. and Odom, A. L., manuscript in preparation.

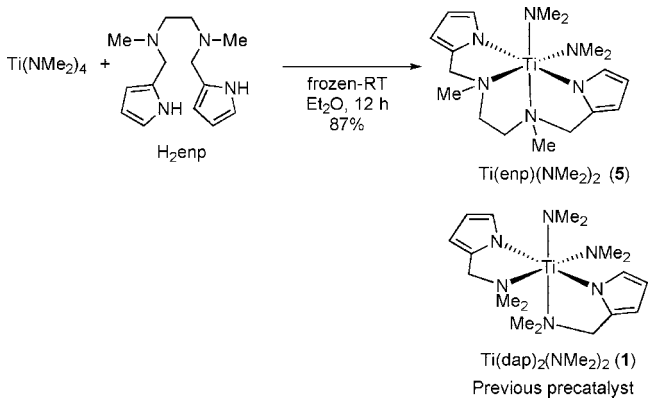
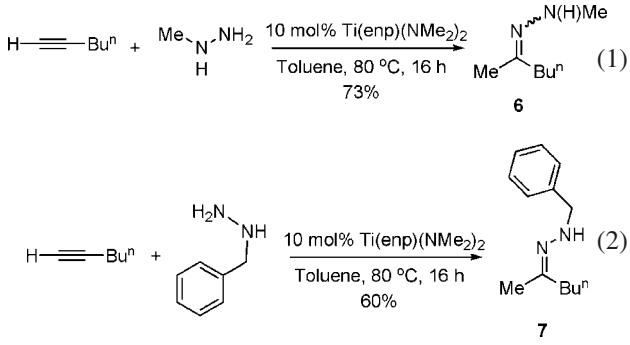


Figure 1. Synthesis of $Ti(enp)(NMe_2)_2$ (**5**) and comparison with $Ti(dap)_2(NMe_2)_2$ (**1**).

reactions using 1-hexyne and phenylhydrazine with 10 mol % catalyst loading at room temperature proceeded to near full conversion, but the reaction rates were impractically slow, requiring ~5 days to reach completion. The reaction of 1-hexyne with phenylhydrazine was optimized to run at 80 °C with 5 mol % **5** and was complete in 2 h.

Under the optimized conditions, reactions were carried out with 5 mol % **5** in toluene at 80 °C for 4.5–41 h (Table 1). Hydrazones of 1-hexyne were obtained in the reaction of methylhydrazine and benzylhydrazine. Only the Markovnikov product was obtained in these cases (eqs 1 and 2). In order to apply this methodology toward indole synthesis, arylhydrazines were allowed to react with different alkynes. In large part for expediency of product isolation and characterization, arylhydrazones (observed by GC/FID and GC/MS) were converted to indoles in a one-pot procedure by excess $ZnCl_2$. In all cases the hydrazones were cleanly generated and observed prior to $ZnCl_2$ addition; consequently, the methodology is generally applicable to hydrazone synthesis.



The regioselectivity of the products was dependent on the electronic and steric properties of the alkyne. Only the Markovnikov product was obtained for the reactions of 1-hexyne with phenylhydrazine (entry 1, Table 1). For the 2-hexyne and phenylhydrazine reaction (entry 2), the apparent hydrohydrazination regioselectivity, based on the ratios of isolated indoles, is 1:4 with a preference for hydrazine addition to the 3-carbon (Scheme 4). If the two alkyl groups (methyl and *n*-propyl) in this alkyne are considered electronically equivalent, this reaction demonstrates the preference of the catalyst to create the new C−N bond at the more hindered carbon in the triple bond.

For symmetrical 3-hexyne, a 1:2.5 mixture of indole products is obtained due to a lack of selectivity in the Fischer indole cyclization (entry 3).

For aryl-substituted alkynes, there is an electronic preference for creation of the new C−N bond β to the phenyl group. Consequently, for phenylacetylene there is a steric preference for addition α to the phenyl group and an electronic preference β to the phenyl group. This leads to a mixture of products for this substrate (entry 6), and the hydrohydrazination reaction with phenylhydrazine resulted in a 1:2.6 mixture favoring the electronically preferred indole from *anti*-Markovnikov addition. Adding even a small amount of sterics to the terminal carbon lessens the steric preference, and for the 1-phenylpropyne reaction the only indole product was from electronically preferred β-addition of hydrazine with respect to the phenyl group (entry 4).

Protected alcohols and amines on the alkyne were employed to provide TBS-protected 2-methyltryptophol and 2-methyl-*N,N*-diethyltryptamine, respectively, after the Fischer indole cyclization (entries 7 and 8).

The effect of using coordinating solvents instead of toluene was also studied. It was found that using THF or acetonitrile as the solvent had no obvious effect on the hydrohydrazination conversion or reactions. In addition, these solvent changes had no obvious effect on the indole cyclization for hydrazones derived from 1-hexyne and phenylhydrazine.

To determine the sensitivity of the titanium catalysis to a variety of potential amine bases, we ran the reaction between 1-hexyne and phenylhydrazine in the presence of several amines. It was observed that there was no significant effect for addition of quiniclidine, triethylamine, 2,6-lutidine, or pyridine. The conversions after 18 h at 80 °C with 10 mol % **5** and 20 mol % base were approximately the same (66–71%) as in the absence of these bases (75%).

From the reaction of 5-chloropent-1-yne with phenylhydrazine two products were obtained (Scheme 5). One product, 3-methyl-1-phenyl-1,4,5,6-tetrahydropyridazine (**17**), was obtained by hydrohydrazination followed by intramolecular elimination of hydrochloric acid and cyclization in situ. The remaining hydrazone **19** undergoes Fisher cyclization, perhaps catalyzed by HCl in the reaction mixture, generating the salt of 2-methyltryptamine (**18**). Free 2-methyltryptamine (**20**) was obtained on basification. Compound **17** was found to be very stable in the presence of HCl generated in the reaction mixture, and also external Lewis acid as observed previously in the literature.[16] The products were obtained in a 1:1 ratio, in an overall yield of 64%.

Addition of 1.1 equiv of triethylamine to a similar reaction between 5-chloropent-1-yne and phenylhydrazine resulted in the formation of two compounds, **17** and **19**, which were observable by GC/MS. Sequential addition of $ZnCl_2$ and NaOH provided 2-methyltryptamine **20** (Scheme 5).

Different substituted phenylhydrazines were also used in reactions with 1-hexyne, and the products were isolated in good yield. Corresponding indoles were obtained when *p*-Me-, *p*-F-, and *p*-OMe-substituted phenylhydrazines were used. Only the products derived from Markovnikov addition to the alkyne were obtained in all of these cases (Table 2).

The scope of the reaction was also extended to diynes. When nona-1,4-diyne was reacted with phenylhydrazine at 80 °C for 16 h in the presence of 5 mol% **5**, substituted dihydropyridazine (**24**) was formed in one step along with a substituted pyrazole product (**25**) (entry 1, Table 3). In this particular case, the dihydropyridazine (**24**) was obtained as the minor product (**24**:**25** 1:2.6). The

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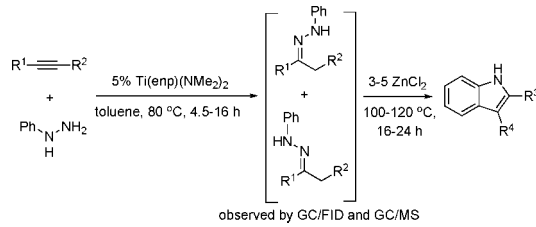
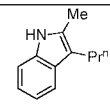
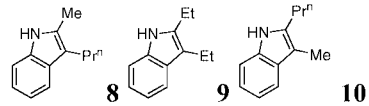
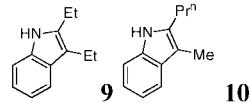
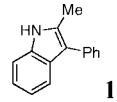
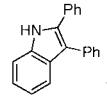
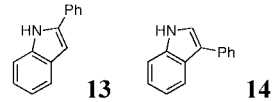
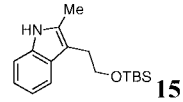
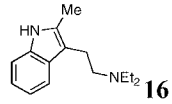
Table 1. Hydrohydrazination of Alkynes with Phenylhydrazine



Entry	R^1	R^2	Product(s)	Ratio (a:b or a:b:c)	Yield (%)[a]
1	H	Bu^n	 **8**	---	87
2	Me	Pr^n	 **8** **9** **10**	1:1.3:2.6	80
3	Et	Et	 **9** **10**	1:2.5	76
4	Me	Ph	 **11**	---	70
5	Ph	Ph	 **12**	---	55
6	H	Ph	 **13** **14**	1:2.6	70
7	H	$(CH_2)_3OTBS$[b]	 **15**	---	62
8	H	$(CH_2)_3NEt_2$	 **16**	---	48

[a] Reaction time for the first step: 16 h for entries 2–4 and 7; 4.5 h for entries 1 and 6; 41 h for entry 5, 24 h for entry 8. [b] TBS = *tert*-butyldimethylsilyl.

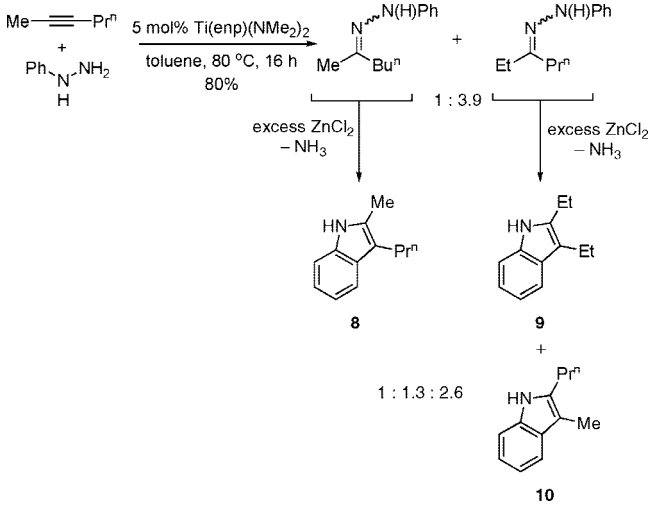
hydrazone generated was due to exclusive addition of the phenylhydrazine in a Markovnikov fashion to the terminal triple bond. The formation of the observed products can be explained as shown in Scheme 6. We speculate that cyclizations may occur through an allene intermediate under the reaction conditions, which can then undergo either 6-*endo* or 5-*exo trig* cyclization, giving rise to **24** or **25**, respectively.[17] An alternative 1,2-insertion pathway involving the alkyne and a titanium hydrazido(1−) of the initial hydrohydrazination product cannot be ruled out under these reaction conditions.[18]

When octa-1,7-diyne was reacted with 2.2 equiv of phenylhydrazine at 100 °C for 24 h, hydrohydrazination at both the triple bonds results. Fischer indole cyclization in one pot furnished 1,2-bis(2-methyl-1*H*-indol-3-yl)ethane[19] in 70% yield (entry 2, Table 3).

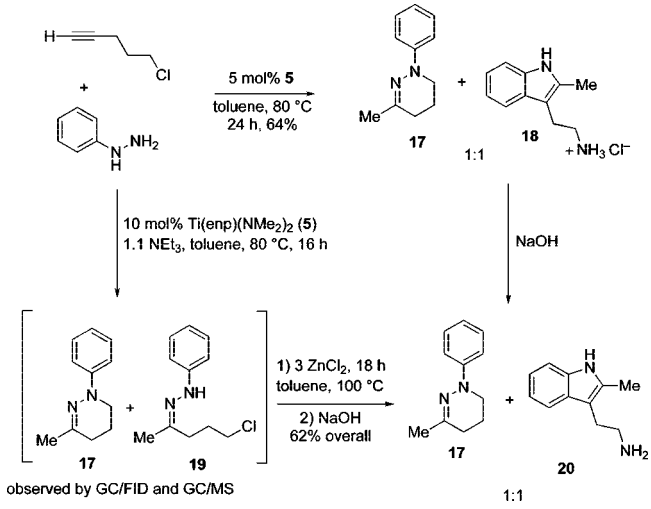
One enyne substrate was examined with phenylhydrazine, 1-ethynylcyclohex-1-ene (entry 3, Table 4). After the formation of the hydrazone, which was not isolated, addition of $ZnCl_2$ resulted in Michael addition of the β-nitrogen of the hydrazone across the C=C bond of the cyclohexenyl moiety to yield the substituted indazole[20] **27** in 52% yield.

(17) (a) Similar dihydropyridazine compounds are known. For references see: Kaneko, C.; Tsuchiya, T.; Igeta, H. *Chem. Pharm. Bull.* **1974**, *22*, 2894–2897. (b) Crossland, I.; Kelstrup, E. *Acta Chem. Scand.* **1968**, *22*, 1669–1676.

Scheme 4. Reaction of 2-Hexyne with Phenylhydrazine Catalyzed by 5

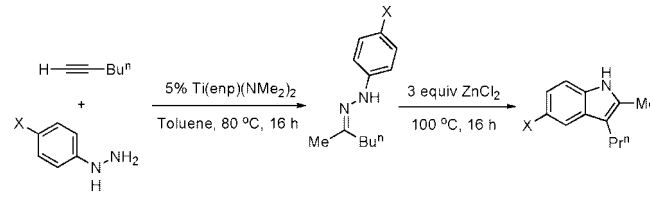


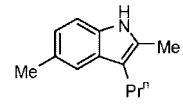
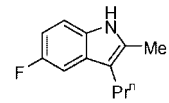
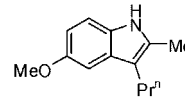
Scheme 5. Hydrohydrazination of 5-Chloropent-1-yne with Phenylhydrazine



Concluding Remarks. A new catalytic hydrohydrazination reaction of monosubstituted hydrazines with alkynes has been developed. This was accomplished by suitably designing the ligand framework on the titanium center. Both terminal and internal alkynes have been used with aliphatic as well as aromatic hydrazines. The regioselectivity of the addition is highly dependent on the electronic and steric nature of the alkyne, and the catalyst is applicable to generating both *N*-alkyl- and *N*-arylhydrazones. This methodology has also been applied to the synthesis of different *NH*-indoles including 2-methyltryptamine and tryptophol derivatives, which are important building blocks of different natural products. As shown above, many different five- and six-membered heterocycles are available using titanium-catalyzed hydrohydrazination.

Table 2. Hydrohydrazination with Substituted Phenylhydrazines



Entry	X	Product	Yield (%)
1	Me	 **21**	64
2	F	 **22**	70
3	OMe	 **23**	76

Experimental Section

General Considerations. All manipulations of air-sensitive compounds were carried out in an MBraun drybox under a purified nitrogen atmosphere. Pentane (Spectrum Chemical Mfg. Corp.), toluene (Spectrum Chemical Mfg. Corp.), ether (Columbus Chemical Industries Inc.), dichloromethane (EM Science), acetonitrile (Spectrum Chemical), and tetrahydrofuran (JADE Scientific) were sparged with nitrogen to remove oxygen then dried by passing through activated alumina. Hydrazines were purchased from Aldrich Chemical Co. and dried by distillation from KOH under dry nitrogen. Alkynes were distilled from CaO under dry nitrogen. Octa-1,7-diyne was purchased from GFS chemicals and distilled over CaO under dry nitrogen. Nona-1,4-diyne[21] and 1-ethynylcyclohex-1-ene[22] were prepared according to the literature procedures. $(BOC)_2O$ (BOC = *tert*-butyloxycarbonyl) and DMAP (4-dimethylaminopyridine) were purchased from Aldrich and used as received. $Ti(NMe_2)_4$[23] was prepared using the literature procedure. The Hdap (where dap = 2-(dimethylaminomethyl)pyrrole) ligand was prepared as described in the literature.[14] Deuterated solvents were dried over purple sodium benzophenone ketyl (C_6D_6) or phosphoric anhydride ($CDCl_3$) and distilled under nitrogen. ^1H and ^{13}C spectra were recorded on Inova-300 or VXR-500 spectrometers. ^1H and ^{13}C assignments were confirmed when necessary with the use of two-dimensional $^1H-^1H$ and $^{13}C-^1H$ correlation NMR experiments. Routine coupling constants in ^{13}C NMR are not reported. All spectra were referenced internally to residual protiosolvent (^1H) or solvent (^{13}C) resonances. Chemical shifts are quoted in ppm, and coupling constants in Hz.

(18) For some examples involving 1,2-insertion of alkynes into transition metal−nitrogen bonds see: Katayev, E.; Li, Y.; Odom, A. L. *Chem. Commun.* **2002**, 838. (b) Boncella, J. M.; Eve, T. M.; Rickman, B.; Abboud, K. A. *Polyhedron* **1998**, *17*, 725. (c) VanderLende, D. D.; Abboud, K. A.; Boncella, J. M. *Inorg. Chem.* **1995**, *34*, 5319. (d) Villanueva, L. A.; Abboud, K. A.; Boncella, J. M. *Organometallics* **1992**, *11*, 2963. (e) Kemmitt, R. D. W.; Mason, S.; Moore, M. R.; Fawcett, J.; Russell, D. R. *Chem. Commun.* **1990**, 1535. Hydroamination of alkynes using lanthanides, for example, also involved 1,2-insertion. For a review see:. (f) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673.

(19) Bergman, J.; Carlsson, R. J. *Heterocycl. Chem.* **1972**, *9*, 833.

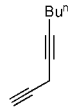
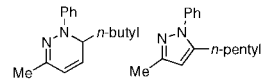
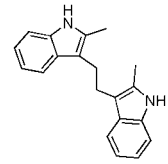
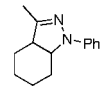
(20) Similar Michael-type reaction is known with acetic acid. For references see: Ferres, H.; Hamdam, M. S.; Jackson, W. R. *J. Chem. Soc., Perkin Trans.* **1973**, *7*, 936–938. (b) Alexander, C. W.; Hamdam, M. S.; Jackson, W. R. *J. Chem. Soc., Chem. Commun.* **1972**, 94–95.

(21) Verkuijsse, H. D.; Hasselaar, M. *Synthesis* **1979**, 292.

(22) Brandsma, L. In *Preparative Acetylenic Chemistry*; Elseim Publishers: Amsterdam, 1971; p 137.

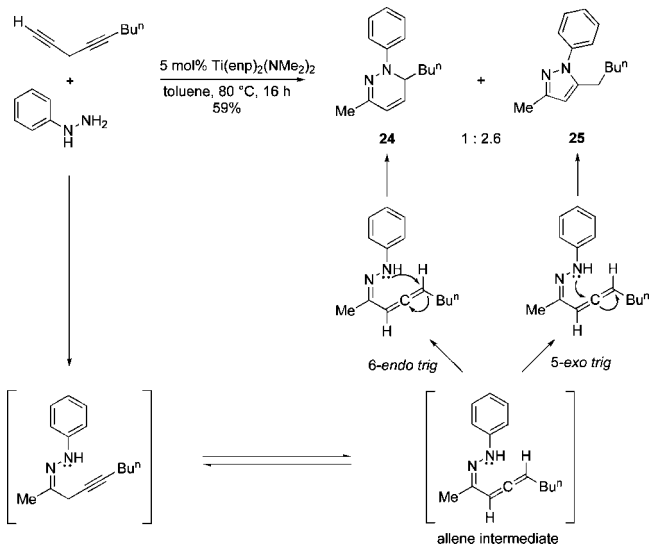
(23) Bradley, D. C.; Thomas, I. M. *J. Chem. Soc.* **1960**, 3859.

Table 3. Hydrohydrazination with Diynes and Enyne

Entry	Substrate	Conditions[a]	Product	Isolated Yield (%)
1		A	 **24** **25**	59[b]
2		B	 **26**	70
3		C	 **27**	52

[a]A is 5 mol % **5** at 80 °C for 16 h, B is 5 mol % **5** at 100 °C for 24 h followed by 4 equiv of $ZnCl_2$ at 100 °C for 24 h, C is 5 mol % **5** at 80 °C for 24 h followed by 3 equiv of $ZnCl_2$ at 100 °C for 36 h. [b]**24**:**25** 1:2.6.

Scheme 6. Possible Pathways to 24 and 25



Synthesis of Butyl-2-((dimethylamino)methyl)-1*H*-pyrrole-1-carboxylate (2). A 500 mL round-bottom flask was charged with Hdap (2.617 g, 21.10 mmol), $(BOC)_2O$ (4.600 g, 21.10 mmol), and DMAP (0.386 g, 3.1 mmol) in dichloromethane (250 mL) and was allowed to stir at room temperature overnight. The solution was quenched with water (20 mL) and extracted with ether (3 × 20 mL). Combined organic layers were washed with water. The organic layer was then dried over $MgSO_4$ and filtered, and volatiles were removed under vacuum. The product was isolated by distillation under vacuum as a colorless oil in 66% yield (3.120 g, 13.90 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (dd, 1 H, J_{HH} = 1.8, 3.4 Hz, 5*H*-pyrrole), 6.11 (m, 1 H, 4*H*-pyrrole), 6.08 (t, J_{HH} = 3.3 Hz, 1 H, 3*H*-pyrrole), 3.65 (s, 2 H, CH_2), 2.26 (s, 6 H, NCH_3), 1.57 (s, 9 H, CCH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.9, 132.7, 121.5, 113.3, 109.7, 83.3, 56.6, 45.5, 28.0. Anal. Experimental (Calc) C: 63.88 (64.26). H: 8.98 (8.99). N: 13.11 (12.49). MS (EI) m/z = 224 (M^+).

Synthesis of [*N*-(*tert*-Butoxycarbonyl)-2-(trimethylaminomethyl)pyrrole]I$^-$ (3). To a 500 mL round-bottom flask was added **2** (9.870 g, 44.00 mmol), methyliodide (6.870 g, 48.40 mmol), and THF (250 mL). The reaction was allowed to stir at room temperature overnight. A white precipitate appeared during the reaction. The precipitate was filtered, washed with THF, and dried under vacuum to yield the product as a white powder in 87% yield (14.00 g, 38.00 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J_{HH} = 3.4 Hz, 1 H, 5*H*-pyrrole), 6.85 (dd, J_{HH} = 1.7, 3.6 Hz, 1 H, 4*H*-pyrrole), 6.27 (t, J_{HH} = 3.4 Hz, 1 H, 3*H*-pyrrole), 5.22 (s, 2 H, CH_2), 3.37 (s, 9 H, NCH_3), 1.58 (s, 9 H, CCH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.4, 125.5, 123.3, 120.9, 111.4, 86.0, 61.4, 52.8, 27.9. Anal. Experimental (Calc) C: 42.81 (42.63). H: 6.52 (6.33). N: 7.75 (7.65). mp 180 °C (dec).

Synthesis of H_2enp (4). A round-bottom flask (500 mL) was charged with K_2CO_3 (7.561 g, 54.80 mmol) in dry acetonitrile (250 mL) and *N*,*N*′-dimethylethylenediamine (0.483 g, 5.50 mmol). To the flask was added **3**(4.091 g, 10.90 mmol). Initially, the reaction was a light brown colored suspension and was refluxed at 105 °C for 2 days. After that, the suspension was allowed to cool to room temperature and sit, producing a brown solution with white precipitate. The mixture was filtered, and the filtrate was dried by rotary evaporation. Ethylacetate was added to the brown oily product, which led to additional white precipitate. The brown solution was filtered, and the filtrate was dried under vacuum. The dark brown resulting oil was subjected to column chromatography on alumina using 60% ethylacetate/pentane followed by 10% MeOH/ethylacetate. The product was isolated as a pale yellow solid in 50% yield (0.670 g, 2.70 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.38 (b, 2 H, N*H*), 6.69 (q, J_{HH} = 2.4 Hz, 2 H, 5*H*-pyrrole), 6.12

(q, J_{HH} = 2.7 Hz, 2 H, 4*H*-pyrrole), 5.99 (m, 2 H, 3*H*-pyrrole), 3.58 (s, 4 H, CH_2-pyrrole), 2.48 (s, 4 H, CH_2CH_2), 2.22 (s, 6 H, CH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 128.9, 117.4, 108.0, 107.0, 54.8, 54.1, 42.8. Mp: 95–97 °C.

Synthesis of Ti(enp)(NMe_2)$_2$ (5). All the manipulations were carried out inside an inert atmosphere glovebox. A filter flask (125 mL) was loaded with Ti(NMe_2)$_4$ (0.388 g, 1.70 mmol) in ether (2 mL) and cooled inside the cold well. To the solution was added cold **4** (0.427 g, 1.70 mmol) in ether (25 mL) dropwise over a period of 15 min. The reaction was allowed to warm to room temperature and stir overnight, producing a dark red solution. Volatiles were removed in vacuo. The product was recystallized from 1:1 ether/pentane as an orange solid in 87% yield (0.560 g, 1.50 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98–7.02 (m, 2 H, 5*H*-pyrrole), 6.10 (app t, J_{HH} = 2.3 Hz, 2 H, 4*H*-pyrrole), 5.80–5.84 (m, 2 H, 3*H*-pyrrole), 4.50 (d, J_{HH} = 15.4 Hz, 2 H, C*H*H-pyrrole), 3.67 (d, J_{HH} = 15.3 Hz, 2 H, CH*H*-pyrrole), 3.38 (s, 12 H, N(CH_3)$_2$), 2.55 (d, J_{HH} = 9.2 Hz, 2 H, C*H*H-C*H*H), 2.14 (d, J_{HH} = 8.8 Hz, 2 H, CH*H*-CH*H*), 1.96 (s, 6 H, CH_2NCH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 138.4, 126.0, 107.0, 99.8, 62.3, 62.1, 49.1, 47.6. Mp: 126–128 °C. Complex **5** after many attempts did not pass elemental analysis. Spectra for the complex are included in the Supporting Information.

Synthesis of *E,Z*-*N*-Methylhydrazones of 2-Hexanone (6a and 6b). Under an inert atmosphere, a threaded pressure tube was charged with **5** (0.050 g, 0.13 mmol) in toluene (1.2 mL), methylhydrazine (136 μL, 2.60 mmol), and 1-hexyne (298 μL, 2.60 mmol). The tube was sealed and taken outside the box for heating at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with ether and passed through a pad of silica in a fritted Büchner funnel. Volatiles from the filtrate were removed in vacuo, and the product was distilled under vacuum (0.1 Torr, 60 °C). The reaction produced a mixture of two isomers, (*E*)-1-(hexan-2-ylidene)-2-methylhydrazine (**6a**, major) and (*Z*)-1-(hexan-2-ylidene)-2-methylhydrazine (**6b**, minor) as a colorless oil in 4.2:1 ratio in 73% combined yield (0.243 g, 1.89 mmol). Isomer **6a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.28 (br s, 1 H, MeN*H*), 2.84 (s, 3 H, H_3CNH), 2.11 (dd, 2 H, J_{HH} = 7.5, 10.0 Hz, C(=N)CH_2), 1.64 (s, 3 H, C(=N)CH_3), 1.36–1.42 (m, 2 H, C(=N)CH$_2$CH_2), 1.21–1.31 (m, 2 H, CH$_3$CH_2), 0.83 (t, 3 H, J_{HH} = 7.0 Hz, CH$_2$CH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.6, 38.7, 38.0, 29.2, 22.3, 13.8. Isomer **6b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.41 (br s, 1 H, MeN*H*), 2.81 (s, 3 H, H_3CNH), 2.05 (dd, 2 H, J_{HH} = 7.5, 8.5 Hz, C(=N)CH_2), 1.83 (s, 3 H, C(=N)CH_3), 1.36–1.42 (m, 2 H, C(=N)CH$_2$CH_2), 1.21–1.31 (m, 2 H, CH$_3$CH_2), 0.86 (t, 3 H, J_{HH} = 7.5 Hz, CH$_2$CH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 150.1, 38.7, 38.1, 27.1, 23.0, 13.9. MS (EI) m/z = 128 (M^+).

Synthesis of the *E*-Benzylhydrazone of 2-Hexanone (7). Under an atmosphere of dry nitrogen, a threaded pressure tube was loaded with **5**(0.057 g, 0.15 mmol) in toluene (750 μL), benzylhydrazine (300 μL, 3.00 mmol), and 1-hexyne (350 μL, 3.00 mmol). The reaction vessel was sealed and removed from the drybox to be heated at 80 °C for 16 h. The solution was then cooled to room temperature, diluted with ether, and passed through a pad of alumina in a fritted funnel. Volatiles were removed from the filtrate under vacuum. The resulting dark brown oil was subjected to column chromatography on alumina using 4:1 hexanes/ethylacetate as eluent. The product was isolated as brown oil in 60% yield (0.360 g, 1.80 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 2 H, *o-H* Ph), 7.31 (d, 2 H, *m-H* Ph), 7.26 (t, 1 H, J_{HH} = 7.1 Hz, *p-H* Ph), 1.36–1.23 (br s, 1 H, N*H*), 4.34 (s, 2 H, NH-CH_2Ph), 2.21 (t, 2 H, J_{HH} = 8.2 Hz, C(=N)CH_2), 1.69 (s, 3 H, C(=N)CH_3), 1.52–1.40 (m, 2 H, J_{HH} = 7.9 Hz, C(=N)CH$_2$CH_2), 1.36–1.22 (m, 2 H, J_{HH} = 8.0 Hz, CH$_3$CH_2), 0.98 (t, 3 H, J_{HH} = 7.5 Hz, CH$_2$CH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.7, 139.6, 128.4, 128.3, 127.1, 55.4, 38.8, 29.1, 22.4, 14.3, 13.9. MS (EI) m/z = 204 (M^+).

Synthesis of 2-Methyl-3-propyl-1*H*-indole (8). Under an atmosphere of dry nitrogen, a threaded pressure tube was loaded with **5** (0.114 g, 0.30 mmol) in toluene (1.5 mL), phenylhydrazine (295 μL, 3.00 mmol), and 1-hexyne (350 μL, 3.00 mmol). The tube was sealed and removed from the drybox for heating at 80 °C for 4.5 h. The reaction was then allowed to cool to room temperature and taken inside the box, and excess $ZnCl_2$ (1.227 g, 9.00 mmol) was added. It was heated at 100 °C for 24 h. After that, the reaction was allowed to cool to room temperature, diluted with ether, and passed through a pad of silica in a fritted funnel. Volatiles were removed from the filtrate in vacuo. The resulting dark brown oil was subjected to column chromatography on silica gel with 7:3 dichloromethane/pentane as eluent. The product[23] was isolated as a pale yellow oil in 87% yield (0.450 g, 2.60 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (br s, 1 H, N*H*), 7.48 (d, 1 H, J_{HH} = 7.5 Hz, 4*H*-indole), 7.24 (dd, 1 H, J_{HH} = 3.5, 6.2 Hz, 7*H*-indole), 7.12 - 7.02 (m, 2 H, 5*H*- and 6*H*-indole), 2.66 (t, 2 H, J_{HH} = 7.5 Hz, CH$_3$CH$_2$CH_2), 2.53 (s, 3 H, 2-CH_3), 1.63 (m, 2 H, CH$_3$CH_2CH$_2$), 0.93 (t, 3 H, J_{HH} = 7.3 Hz, CH_3CH$_2$). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 135.3, 130.7, 128.9, 120.7, 118.9, 118.2, 112.3, 110.0, 26.2, 23.8, 14.1, 11.7. MS (EI) m/z = 173 (M^+).

Reaction of 3-Hexyne with Phenylhydrazine to Form 9 and 10. Under an inert atmosphere, a threaded pressure tube was charged with Ti(enp)(NMe_2)$_2$ (0.050 g, 0.13 mmol) in toluene (1.2 mL), phenylhydrazine (255 μL, 2.60 mmol), and 3-hexyne (296 μL, 2.60 mmol). The tube was sealed and removed from the drybox for heating at 80 °C for 16 h. After cooling to room temperature, the tube was charged (in the box) with $ZnCl_2$ (1.060 g, 7.80 mmol) and heated at 100 °C for 24 h. The reaction mixture was diluted with ether and passed through a pad of silica in a fritted funnel. Volatiles were removed from the filtrate in vacuo, and the resulting brown oil was subjected to column chromatography on silica gel with 1:1 dichloromethane/pentane as eluent. The reaction produced a mixture of two isomers, 3-methyl-2-propyl-1*H*-indole[24] (**10**, major) and 2,3-diethyl-1*H*-indole (**9**, minor), in a 2.5:1 ratio. The product coeluted from the column as a pale yellow oil in 76% combined yield (0.340 g, 1.97 mmol). Isomer **9**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (br s, 1 H, N*H*), 7.56 (d, 1 H, J_{HH} = 7.5 Hz, 4*H*-indole), 7.28 (d, 1 H, J_{HH} = 7.0 Hz, 7*H*-indole), 7.15–7.08 (m, 2 H, 5*H*- and 6*H*-indole), 2.75 (m, 4 H, 2- and 3-CH_2), 1.27 (m, 6 H, 2- and 3-CH$_2$CH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 135.2, 135.1, 128.4, 120.8, 118.2, 118.0, 113.1, 110.2, 19.3, 17.3, 15.8, 14.5. MS (EI) m/z = 173 (M^+). Isomer **10**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (br s, 1 H, N*H*), 7.50 (d, 1 H, J_{HH} = 7.5 Hz, 4*H*-indole), 7.27 (d, 1 H, J_{HH} = 7.0 Hz, 7*H*-indole), 7.15–7.08 (m, 2 H, 5*H*- and 6*H*-indole), 2.70 (t, 2 H, J_{HH} = 7.0 Hz, 2-CH_2), 2.26 (s, 3 H, 3-CH_3), 1.69 (m, 2 H, CH$_3$CH_2), 0.99 (t, 3 H, J_{HH} = 7.5 Hz, CH$_2$CH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 136.0, 135.1, 129.3, 120.8, 118.9, 118.0, 110.1, 106.9, 28.1, 23.0, 13.8, 8.4. MS (EI) m/z = 173 (M^+).

Reaction of 2-Hexyne with Phenylhydrazine to Form 8, 9, and 10. Under an inert atmosphere, a threaded pressure tube was charged with **5** (0.050 g, 0.13 mmol) in toluene (1.2 mL), phenylhydrazine (255 μL, 2.6 mmol), and 2-hexyne (296 μL, 2.6 mmol). The tube was sealed and removed from the drybox for heating at 80 °C for 16 h. After cooling to room temperature, the tube was charged (in the box) with $ZnCl_2$ (1.060 g, 7.80 mmol) and heated at 100 °C for 24 h. The reaction mixture was diluted with ether and passed through a pad of silica in a fritted funnel. Volatiles were removed from the filtrate in vacuo, and the resulting brown oil was subjected to column chromatography on silica gel with 1:1 dichloromethane/pentane as eluent. The reaction produced a mixture of the three isomers 3-methyl-2-propyl-1*H*-indole (**10**, major), 2,3-diethyl-1*H*-indole (**9**, minor), and 2-methyl-3-propyl-

(24) Jackson, A. H.; Smith, A. E. *Tetrahedron* **1965**, *21*, 989.
(25) Baccolini, G.; Bartoli, G.; Marotta, E.; Todesco, P. E. *J. Chem. Soc., Perkin Trans.* **1983**, *11*, 2695.

1*H*-indole (**8**, minor) in 2.6:1.3:1 ratio. The products coelute as a pale yellow oil in 80% combined yield (0.360 g, 2.07 mmol). See above for spectral details.

Synthesis of 2-Methyl-3-phenyl-*NH*-indole (11). Under an inert atmosphere, a threaded pressure tube was charged with **5** (0.050 g, 0.13 mmol) in toluene (1.2 mL), phenylhydrazine (255 μL, 2.60 mmol), and 1-phenylpropyne (325 μL, 2.60 mmol). The tube was sealed and removed from the drybox for heating at 80 °C for 16 h. After cooling to room temperature, the tube was charged (in the box) with $ZnCl_2$ (1.060 g, 7.80 mmol) and heated at 100 °C for 24 h. The reaction mixture was diluted with ether and passed through a pad of silica in a fritted funnel. Volatiles were removed from the filtrate in vacuo, and the resulting brown oil was subjected to column chromatography on alumina gel with 2:1 dichloromethane/pentane as eluent. The product, 2-methyl-3-phenyl-1*H*-indole[26] (**11**), came out as a colorless oil in 70% yield (0.376 g, 1.82 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (br s, 1 H, N*H*), 7.70 (d, 1 H, J_{HH} = 8.0 Hz, 7*H*-indole), 7.53 (m, 2 H, *o*-Ph), 7.48 (m, 2 H, *m*-Ph), 7.33 (m, 1 H, *p*-Ph), 7.31 (m, 1 H, 4*H*-indole), 7.19 (td, 1 H, J_{HH} = 1.5, 7.0 Hz, 5*H*-indole), 7.14 (td, 1 H, J_{HH} = 1.0, 7.0 Hz, 6*H*-indole), 2.49 (s, 3 H, 2-CH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 135.4, 135.2, 131.4, 129.4, 128.5, 127.8, 125.8, 121.5, 119.9, 118.7, 114.4, 110.3, 12.4. MS (EI) *m*/*z* = 207 (M^+).

Synthesis of 2,3-Diphenyl-1*H*-indole (12). Under an inert atmosphere, a threaded pressure tube was charged with **5** (0.100 g, 0.26 mmol) in toluene (1.2 mL), phenylhydrazine (255 μL, 2.60 mmol), and diphenylacetylene (0.463 g, 2.60 mmol). The tube was sealed and removed from the drybox for heating at 100 °C for 41 h. After cooling to room temperature, the tube was charged (in the box) with $ZnCl_2$ (1.060 g, 7.80 mmol) and heated at 100 °C for 24 h. The reaction mixture was diluted with ether and passed through a pad of silica in a fritted funnel. Volatiles were removed from the filtrate in vacuo, and the resulting brown oil was subjected to column chromatography on alumina with 4:1 dichloromethane/pentane as eluent. The product, 2,3-diphenyl-1*H*-indole (**12**),[25] was isolated as a yellow solid in 55% yield (0.384 g, 1.43 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (br s, 1 H, N*H*), 7.67–7.61 (m, 2 H, Ph), 7.43–7.21 (m, 11 H, Ph), 7.13 (m, 1 H, Ph). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 135.9, 135.4, 135.2, 135.0, 134.1, 132.7, 131.4, 130.1, 129.3, 128.7, 128.5, 128.1, 127.7, 126.2, 122.7, 120.4, 119.7, 112.7, 110.9. MS (EI) *m*/*z* = 269 (M^+).

Synthesis of 2-Phenylindole (13) and 3-Phenylindole (14). Under an atmosphere of dry nitrogen, a threaded pressure tube was loaded with **5**(0.093 g, 0.25 mmol) in toluene (1.2 mL), phenylhydrazine (518 μL, 4.90 mmol), and phenylacetylene (538 μL, 4.90 mmol). The tube was sealed and removed from the drybox for heating at 80 °C for 4.5 h. The reaction was then allowed to cool to room temperature and taken inside the box, and excess $ZnCl_2$ (3.279 g, 24.50 mmol) was added. The tube then was heated at 120 °C for 24 h. After that, the mixture was allowed to cool to room temperature, diluted with ether, and passed through a pad of silica in a fritted funnel. Volatiles were removed from the filtrate in vacuo. The resulting dark brown oil was subjected to column chromatography on silica gel with 1:1 petroleum ether/ether as eluent. The products[27] were isolated as a pale yellow oil in 70% yield (0.660 g, 2.60 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (br s, 1 H, N*H*), 8.38 (br s, 1 H, N*H*), 7.95 (s, 1 H, 2-C*H*), 7.78–7.15 (m, 9 H, Ph), 7.38–7.18 (m, 9 H, Ph) 6.81 (s, 1 H, 3-C*H*). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 137.9, 136.8, 136.6, 135.5, 132.4, 129.3, 129.0–125.1, 122.4–119.8, 118.4, 113.2, 111.4, 110.9, 100.0. MS (EI) *m*/*z* = 193 (M^+).

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Synthesis of 2-Methyl-3-(2-(dimethyl(*tert*-butyl)siloxy)ethyl)indole (15). Under an atmosphere of dry nitrogen, a threaded pressure tube was loaded with **5** (0.024 g, 0.07 mmol) in toluene (315 μL), phenylhydrazine (124 μL, 1.30 mmol), and (pent-4-ynyloxy)*t*-butyldimethylsilane (0.250 g, 1.30 mmol). The tube was sealed and removed from the drybox for heating at 80 °C for 16 h. The solution was then allowed to cool to room temperature and taken inside the box, and excess $ZnCl_2$ (0.506 g, 3.90 mmol) was added. The reaction was heated at 100 °C for 16 h. The mixture was allowed to cool to room temperature, diluted with ether, and passed through a pad of silica in a fritted funnel. Volatiles were removed from the filtrate in vacuo. The resulting dark red oil was subjected to column chromatography on silica gel with 7:3 hexanes/ethylacetate as eluent. The product was isolated as a pale yellow oil in 62% yield (0.220 g, 0.80 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (br s, 1 H, N*H*), 7.52 (d, 1 H, J_{HH} = 7.4 Hz, 7*H*-indole), 7.28 (d, 1 H, J_{HH} = 6.9 Hz, 4*H*-indole), 7.17 (m, 2 H, 5*H*- and 6*H*-indole), 3.65 (t, 2 H, J_{HH} = 8.9 Hz, OCH_2), 2.98 (t, 2 H, J_{HH} = 7.4 Hz, OCH$_2$CH_2), 2.41 (s, 3 H, 2-CH_3), 0.86 (s, 9 H, CCH_3), 0.11 (s, 6 H, SiCH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 135.2, 131.7, 128.9, 120.9, 119.1, 117.9, 110.1, 108.4, 63.6, 28.2, 26.0, 18.4, 11.7, –5.3. MS (EI) *m*/*z* = 289 (M^+).

Synthesis of *N*,*N*-Diethyl-2-methyltryptamine (16). To synthesize the alkyne, a 250 mL round-bottom flask was charged with 5-chloropent-1-yne (2 g, 19.6 mmol), diethylamine (1.79 g, 24.5 mmol), and toluene (70 mL). The reaction mixture was heated at 95 °C for 36 h. After cooling to room temperature, the reaction was quenched with HCl (6 M), and the mixture was extracted with water (3 × 20 mL). The combined aqueous phase was basified with KOH solution (1 M), and the product was extracted with ether (3 × 30 mL). The combined organic phase was dried over $MgSO_4$ and filtered, and ether was removed using rotory evaporation using an ice/water bath. The product was distilled using a water aspirator (15 Torr, 42 °C) to yield *N,N*-diethylpent-4-yn-1-amine (0.436 g, 3.13 mmol) as a pale yellow oil in 16% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.43–2.48 (m, 6 H, NCH_2CH$_2$ and NCH_2CH$_3$), 2.16 (td, 2 H, J_{HH} = 7.0 and 2.5 Hz, propargyl CH_2), 1.89 (t, 1 H, J_{HH} = 2.5 Hz, C*H*), 1.58–1.64 (m, 2 H, CH$_2$CH_2CH$_2$), 0.97 (t, 6 H, J_{HH} = 7 Hz, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ 84.4, 68.1, 51.6, 47.0, 26.1, 16.4, 11.8.

Under an inert atmosphere, a threaded pressure tube was charged with **5** (0.05 g, 0.13 mmol) in toluene (1.2 mL), phenylhydrazine (255 μL, 2.60 mmol), and *N,N*-diethylpent-4-yn-1-amine (0.361 g, 2.60 mmol). The tube was sealed and removed from the drybox for heating at 80 °C for 24 h. After cooling to room temperature, the tube was charged (in the box) with $ZnCl_2$ (1.060 g, 7.80 mmol) and heated at 100 °C for 36 h. The reaction mixture was diluted with ether and ethylacetate. The solution was then passed through a pad of silica in a fritted funnel. Volatiles were removed from the filtrate in vacuo, and the resulting brown oil was subjected to column chromatography on alumina with 10:1 ethylacetate/methanol as eluent. The product, *N,N*-diethyl-2-methyltryptamine (**16**), was isolated as a brown solid in 48% yield (0.287 g, 1.25 mmol). This compound is insoluble in dichloromethane or chloroform. ^{1}H NMR (500 MHz, $(CD_3)_2CO$): δ 7.52 (d, 1 H, J_{HH} = 7.5 Hz, 7*H*-indole), 7.30 (d, 1 H, J_{HH} = 7.0 Hz, 4*H*-indole), 7.01 (t, 1 H, J_{HH} = 7.0 Hz, 5*H*-indole), 6.96 (t, 1 H, J_{HH} = 7.0 Hz, 6*H*-indole), 6.83 (br s, 1 H, N*H*), 3.54 (m, 4 H, NCH_2CH$_3$), 3.47 (m, 2 H, NCH_2CH$_2$), 3.26 (dd, 2 H, J_{HH} = 5.5, 8.5 Hz, NCH$_2$CH_2), 2.42 (s, 3 H, 2-CH_3), 1.40 (t, 6 H, J_{HH} = 7.0 Hz, NCH$_2$CH_3). ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2CO$): δ 135.1, 132.7, 127.4, 120.1, 118.4, 116.7, 110.1, 103.8, 51.6, 47.1, 18.6, 10.3, 7.9. MS (EI) *m*/*z* = 230 (M^+).

Synthesis of 1-Phenyl-3-methyltetrahydropyridazine (17). Under an atmosphere of dry nitrogen, a threaded pressure tube was loaded with **5**(0.139 g, 0.37 mmol) in toluene (1.8 mL), phenylhydrazine (717 μL, 7.30 mmol), and 5-chloropent-1-yne (775 μL, 7.30 mmol). The tube was sealed and removed from the drybox

for heating at 80 °C for 24 h. The reaction was then allowed to cool to room temperature and diluted with dichloromethane (20 mL), and saturated $NaHCO_3$ solution was added. The organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organics were washed with water, and the final combined organics were dried over $MgSO_4$, filtered, and dried in vacuo. This yielded a dark brown oil, which was subjected to column chromatography on silica gel using 4:1 petroleum ether/ether as eluent. The product[28] was isolated in 32% yield (0.400 g, 2.30 mmol) as a yellow oil, which turned to red on standing. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (t, 2 H, J_{HH} = 4.1 Hz, 8.7 Hz, *o*-Ph), 7.22 (d, 2 H, J_{HH} = 7.8 Hz, *m*-Ph), 6.87 (t, 1 H, J_{HH} = 7.4 Hz, *p*-Ph), 3.51 (t, 2 H, J_{HH} = 6.1 Hz, NCH_2), 2.21 (t, 3 H, J_{HH} = 6.1 Hz, C(=N)CH_2), 2.08 (m, 2 H, (=N)CH_2CH_2), 2.02 (s, 3 H, CH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 148.3, 143.6, 128.8, 119.1, 113.5, 42.2, 25.6, 24.3, 19.0. MS (EI) *m*/*z* = 174 (M^+).

Synthesis of 2-Methyltryptamine (20). Under an atmosphere of dry nitrogen, a threaded pressure tube was loaded with **5** (0.185 g, 0.49 mmol) in toluene (2.4 mL), phenylhydrazine (964 μL, 9.80 mmol), and 5-chloropent-1-yne (1034 μL, 9.80 mmol). The tube was sealed and removed from the drybox for heating at 80 °C for 24 h. The reaction then was allowed to cool to room temperature. The hydrochloride salt (**18**) of the product precipitated during reaction. The precipitate was washed with ethylacetate (50 mL), which contained crude **17**. To the crude **18** was added NaOH (20%, 25 mL), and the product was extracted with ethylacetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and volatiles were removed under vacuum. To the resulting brown oil was added hexanes (20 mL) and then HCl in ether until it reached pH ~2. A brown solid precipitated from the solution. The solid was filtered, and volatiles were again removed under vacuum. Next, the solids were dissolved in dichloromethane (20 mL), and saturated $NaHCO_3$ solution was added to the solution (pH ~7). The mixture was shaken, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with water. The final organic layer was dried over $MgSO_4$ and filtered, and volatiles were removed in vacuo. This yielded **20** as a brown solid[28] in 32% yield (0.400 g, 2.30 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (br s, 1 H, N*H*), 7.85 (d, 1 H, J_{HH} = 8.1 Hz, 7*H*-indole), 7.26 (d, 1 H, J_{HH} = 5.6 Hz, 4*H*-indole), 7.18–7.04 (m, 2 H, 5*H*- and 6*H*-indole), 2.96 (t, 2 H, J_{HH} = 6.6 Hz, 3-CH_2), 2.84 (t, 2 H, J_{HH} = 6.6 Hz, NH_2CH_2), 2.38 (s, 3 H, 2-CH_3), 1.74 (br s, 2 H, NH_2). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 135.3, 131.8, 128.8, 121.0, 119.2, 118.0, 110.2, 109.0, 42.5, 28.0, 11.8. MS (EI) *m*/*z* = 174 (M^+).

Synthesis of 2,5-Dimethyl-3-propyl-*NH*-indole (21). Under an atmosphere of dry nitrogen, a threaded pressure tube was loaded with **5**(0.029 g, 0.08 mmol) in toluene (375 μL), *p*-methylphenylhydrazine (0.183 g, 1.50 mmol), and 1-hexyne (175 μL, 1.50 mmol). The tube was sealed and removed from the drybox for heating at 80 °C for 16 h. The solution was then allowed to cool to room temperature and taken inside the box, and excess $ZnCl_2$ (0.602 g, 4.50 mmol) was added. The reaction was heated at 100 °C for 16 h. After that, the solution was allowed to cool to room temperature, diluted with ether, and passed through a pad of silica in a fritted funnel. Volatiles were removed from the filtrate in vacuo. The resulting dark red oil was subjected to column chromatography on silica gel with 1:1 hexanes/ethylacetate as eluent. The product was isolated as a red solid in 64% yield (0.180 g, 0.90 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (br s, 1 H, N*H*), 7.26 (s, 1 H, 4*H*-indole), 7.13 (d, 1 H, J_{HH} = 8.1 Hz, 6*H*-indole), 6.91 (dd, 1 H, J_{HH} = 1.4, 8.1 Hz, 7*H*-indole), 2.61 (t, 2 H, J_{HH} = 7.3 Hz, 3-CH_2), 2.43 (s, 3 H, 5-CH_3), 2.33 (s, 3 H, 2-CH_3), 1.63 (m, 2 H, CH_3CH_2), 0.94 (t, 3 H, J_{HH} = 7.4 Hz, CH_2CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 133.5, 130.9, 129.1, 128.0, 122.2, 118.0, 111.9, 109.7, 26.2, 23.8, 21.5, 14.1, 11.7. MS (EI) *m*/*z* = 187 (M^+).

Synthesis of 2-Methyl-5-fluoro-3-propyl-*NH*-indole (22). Under an atmosphere of dry nitrogen, a threaded pressure tube was loaded with **5** (0.029 g, 0.08 mmol) in toluene (375 μL), *p*-fluorophenylhydrazine (0.192 g, 1.50 mmol), and 1-hexyne (175 μL, 1.50 mmol). The tube was sealed and removed from the drybox for heating at 80 °C for 16 h. The reaction then was allowed to cool to room temperature and taken inside the box, and excess $ZnCl_2$ (0.602 g, 4.50 mmol) was added. The mixture was heated at 100 °C for 16 h. After that, the reaction was allowed to cool to room temperature, diluted with ether, and passed through a pad of silica in a fritted funnel. Volatiles were removed from the filtrate in vacuo. The resulting dark red oil was subjected to column chromatography on silica gel with 2:1 ether/pentane as eluent. The product was isolated as a red oil in 70% yield (0.200 g, 1.05 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (br s, 1 H, N*H*), 7.17–7.15 (dd, 1 H, J_{HH} = 2.5, 9.9 Hz, 4*H*-indole), 7.14–7.11 (dd, 1 H, J_{HH} = 4.4, 8.6 Hz, 7*H*-indole), 6.87−6.83 (dt, 1 H, J_{HH} = 2.5, 9.0 Hz, 6*H*-indole), 2.63 (t, 2 H, J_{HH} = 7.7 Hz, 3-CH_2), 2.35 (s, 3 H, 2-CH_3), 1.63 (m, 2 H, CH_3CH_2), 0.95 (t, 3 H, J_{HH} = 6.5 Hz, CH_2CH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.6, 156.7, 132.9, 129.3 (d, J_{CF} = 9.7 Hz), 112.5 (d, J_{CF} = 4.5 Hz), 110.5 (d, J_{CF} = 9.7 Hz), 108.7 (d, J_{CF} = 26.2 Hz), 103.3, (d, J_{CF} = 23.6 Hz), 26.1, 23.7, 14.0, 11.7. Anal. Experimental (Calc) C: 75.04 (75.36). H: 7.65 (7.38). N: 7.18 (7.32). MS (EI) *m*/*z* = 191 (M^+).

Synthesis of 2-Methyl-5-methoxy-3-propyl-*NH*-indole (23). Under an atmosphere of dry nitrogen, a threaded pressure tube was loaded with **5** (0.057 g, 0.15 mmol) in toluene (750 μL), *p*-methoxyphenylhydrazine (0.421 g, 3.0 mmol), and 1-hexyne (350 μL, 3.0 mmol). The tube was sealed and removed from the drybox for heating at 80 °C for 16 h. The reaction then was allowed to cool to room temperature and taken inside the box, and excess $ZnCl_2$ (0.602 g, 9.00 mmol) was added. The mixture was heated at 100 °C for 16 h. After that, the reaction was allowed to cool to room temperature, diluted with ether, and passed through a pad of silica in a fritted funnel. Volatiles were removed from the filtrate in vacuo. The resulting dark brown-red oil was subjected to column chromatography on silica gel with 1:1 hexanes/ethylacetate as eluent. The product was isolated as a red oil in 76% yield (0.460 g, 2.30 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (br s, 1 H, N*H*), 7.25 (d, 1 H, J_{HH} = 8.8 Hz, 7*H*-indole), 6.94 (d, 1 H, J_{HH} = 2.5 Hz, 4*H*-indole), 6.76–6.72 (dd, 1 H, J_{HH} = 2.5, 8.5 Hz, 6*H*-indole), 3.85 (s, 3H, OCH_3), 2.62 (t, 2 H, J_{HH} = 7.4 Hz, 3-CH_2), 2.32 (s, 3 H, 2-CH_3), 1.68–1.59 (m, 2 H, CH_3CH_2), 0.96 (t, 3 H, J_{HH} = 7.4 Hz, CH_2CH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 153.7, 131.8, 130.4, 129.3, 112.1, 110.6, 110.2, 100.9, 56.0, 26.2, 23.7, 14.1, 11.8. Anal. Experimental (Calc) C: 76.62 (76.81). H: 8.85 (8.43). N: 6.34 (6.89). MS (EI) *m*/*z* = 203 (M^+).

Reaction of 1,4-Nonadiyne with Phenylhydrazine to Synthesize 24 and 25. Under an atmosphere of dry nitrogen, a threaded pressure tube was loaded with **5** (0.040 g, 0.11 mmol) in toluene (525 μL), phenylhydrazine (204 μL, 2.10 mmol), and nona-1,4-diyne (0.250 g, 2.10 mmol). The tube was sealed and removed from the drybox for heating at 80 °C for 16 h. The reaction was then allowed to cool to room temperature, diluted with ether, and passed through a pad of alumina in a fritted funnel. Volatiles were removed from the filtrate in vacuo. The resulting dark red oil was subjected to column chromatography on alumina. Isomer **24** eluted with 5:1 hexanes/ether as the first fraction. After removing volatiles in vacuo, **24** was isolated in 17% yield (0.080 g, 0.35 mmol). Isomer **25** eluted using 1:1 hexanes/ether in the second fraction. After removing volatiles in vacuo, **25** was isolated in 42% yield (0.203 g, 0.89 mmol). Isomer **24**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26–7.19 (m, 4 H, *o,m*-Ph), 6.83 (t, 1 H, J_{HH} = 7.0 Hz, *p*-Ph), 6.04 (dd, 1 H, J_{HH} = 6.6, 9.3 Hz, 5*H*-pyridazine), 5.87 (d, 1 H, J_{HH} = 9.9 Hz, 4*H*-

(28) Benincori, T.; Brenna, E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2139.

pyridazine), 4.62 (m, 1 H, 6*H*-pyridazine), 2.06 (s, 3 H, 3-CH_3), 1.61–1.47 (m, 2 H, 6-CH_2), 1.28 (m, 4 H, CH_3CH_2 and $CH_3CH_2CH_2$), 0.84 (t, J_{HH} = 6.9 Hz, 3H, CH_3CH_2). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 146.0, 142.8, 129.0, 127.4, 120.0, 119.6, 113.7, 51.0, 30.6, 26.2, 22.7, 21.2, 14.0. MS (EI) m/z = 228 (M^+). Isomer **25**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.46–7.32 (m, 5 H, Ph), 6.00 (s, 1 H, 4*H*-pyrazole), 2.58 (t, 2 H, J_{HH} = 8.0 Hz, 5-CH_2), 2.29 (s, 3 H, 3-CH_3), 1.55 (m, 2 H, CH_2CH_2), 1.25 (m, 4 H, $CH_3CH_2CH_2$ and $CH_3CH_2CH_2$), 0.84 (t, 3 H, J_{HH} = 7.1 Hz, CH_2CH_3). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 148.9, 144.6, 140.0, 129.0, 127.4, 125.3, 105.2, 31.4, 28.5, 26.2, 22.3, 13.9, 13.6. MS (EI) m/z = 228 (M^+).

Synthesis of 1,2-Bis(2-methyl-1*H*-indol-3-yl)ethane (26). Under an inert atmosphere, a threaded pressure tube was charged with **5** (0.100 g, 0.26 mmol) in toluene (1.2 mL), phenylhydrazine (561 μL, 5.70 mmol), and 1,7-octadiyne (336 μL, 2.60 mmol). The tube was sealed and removed from the drybox for heating at 100 °C for 24 h. After cooling to room temperature, the tube was charged (in the box) with $ZnCl_2$ (1.410 g, 10.40 mmol) and heated at 100 °C for 24 h. The reaction mixture was diluted with ether and passed through a pad of silica in a frit. The filtrate was dried under vacuum, and the resulting brown oil was subjected to column chromatography on alumina with 1:1 dichloromethane/pentane as eluent. The product, 1,2-bis(2-methyl-1*H*-indol-3-yl)ethane,[30] was isolated as a pale yellow solid in 70% yield (0.520 g, 1.82 mmol). **26** is partially soluble in chlorinated solvents and insoluble in water and acetone. The compound can also be crystallized from acetone/pentane. ^1H NMR (500 MHz, $CDCl_3$): δ 7.62 (br s, 2 H, N*H*), 7.50 (d, 2 H, J_{HH} = 7.5 Hz, 7*H*-indole), 7.23 (d, 2 H, J_{HH} = 7.0 Hz, 4*H*-indole), 7.12–7.04 (m, 4 H, 5*H*- and 6*H*-indole), 2.95 (s, 4 H, 3-CH_2), 2.04 (s, 6 H, 2-CH_3). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 135.2, 131.1, 128.7, 120.7, 119.0, 117.9, 111.9, 110.0, 25.2, 11.2. MS (EI) m/z = 288 (M^+). This compound was also characterized by X-ray diffraction. See the Supporting Information for details.

Reaction of 3-Ethynylcyclohex-1-ene with Phenylhydrazine to Synthesize 27. Under an inert atmosphere, a threaded pressure tube was charged with **5** (0.100 g, 0.26 mmol) in toluene (1.2 mL), phenylhydrazine (255 μL, 2.60 mmol), and 3-ethynylcyclohex-1-ene (275 μL, 2.60 mmol). The tube was sealed and removed from the drybox for heating at 100 °C for 16 h. After cooling to room temperature, the tube was charged (in the box) with $ZnCl_2$ (1.050 g, 7.80 mmol) and heated at 100 °C for 24 h. The reaction mixture was diluted with ether and passed through a pad of silica in a fritted funnel. Volatiles were removed from the filtrate in vacuo, and the resulting brown oil was subjected to column chromatography on alumina with 2:1 dichloromethane/pentane as eluent. The product[31] was isolated as a pale yellow oil in 52% yield (0.289 g, 1.35 mmol). ^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (t, 2 H, J_{HH} = 7.5 Hz, *m*-Ph), 7.07 (d, 2 H, J_{HH} = 7.0 Hz, *o*-Ph), 6.80 (t, 1 H, J_{HH} = 7.0 Hz, *p*-Ph), 4.19 (m, 1 H, PhNC*H*), 3.02 (m, 1 H, MeCC*H*), 2.04 (s, 3 H, 3-CH_3), 1.88 (m, 2 H, 4*H*-indazole), 1.74 (m, 2 H, 7*H*-indazole), 1.59 (m, 2 H, 6*H*-indazole), 1.18 (m, 2 H, 5*H*-indazole). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 153.7, 145.8, 128.9, 119.0, 114.9, 59.9, 47.2, 24.2, 23.2, 22.6, 21.6, 14.0. MS (EI) m/z = 214 (M^+).

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Supporting Information Available: ^1H and ^{13}C NMR spectra of many of the organic compound and crystallographic tables for the structural determination on **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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