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Metal-free, Mild, and Selective Synthesis of *Bis*(pyrazolyl)alkanes by Nucleophile-Catalyzed Condensation

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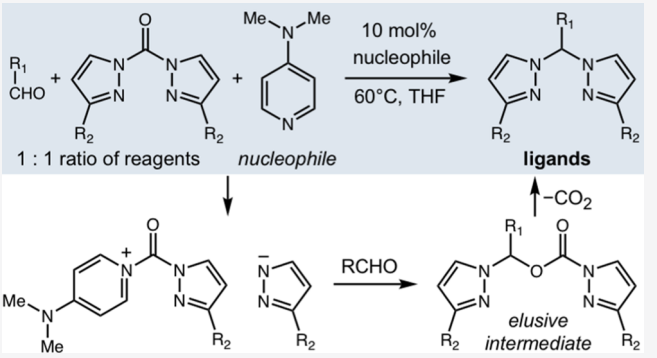
ABSTRACT: *Bis*(pyrazolyl)alkanes are a prolific class of ligands for catalysis, accessible by the condensation between *bis*(pyrazolyl)methanones and carbonyls. In this report, we describe a nucleophile-catalyzed innovation on this condensation that avoids the transition metals, high temperatures, reagent excess, and air-sensitive reagents common among the existing protocols. Significantly, this method accommodates sterically hindered and electronically diverse pyrazoles and aldehydes, applicable for systematic ligand optimization. Furthermore, our scope includes azoles and bridging functional groups previously unreported for this reaction, promising for new heteroscorpionate catalysts. We provide the first direct evidence for an elusive reaction intermediate and characterize the most complete mechanism for this condensation.



INTRODUCTION

Single-site metal−ligand complexes have revolutionized the application and mechanistic understanding of organometallic catalysis. Their primary role is to provide discrete kinetics and structural modularity as the basis for the rational design, analysis, and optimization of catalysts.[1] In this effort, pyrazole-based ligands are particularly useful because of the availability of pyrazoles bearing sterically, functionally, and electronically diverse substituents. In particular, *bis*(pyrazolyl)alkanes[2] have been fashioned into a diverse range of heteroscorpionate ligands.[3] Their transition[4] and main group[5] metal complexes have been extensively studied as catalysts for a wide range of reactions including ethylene trimerization,[6] transfer hydrogenation,[7] and C−H amination (Scheme 1, top).[8] Furthermore, their tripodal arrangement of weak field ligands constitutes an enzyme-like coordination environment ideal for biomimetic catalysis and modeling.[9]

Although simple *bis*(pyrazolyl)methane ligands are prepared straightforwardly by nucleophilic substitution on dihaloalkanes,[10] this strategy often fails for more elaborate *bis*(pyrazolyl)alkanes because of either inefficient substitution or precursor synthesis. Addressing this limitation, Thé and Peterson developed a metal-catalyzed condensation reaction between carbonyls and either *bis*(pyrazolyl)methanones[11] or sulfinyldipyrazoles[12] that deliver *bis*(pyrazolyl)alkanes substituted at the linking carbon (Scheme 1). Their method is atom-economical and operationally simple, but requires an excess of carbonyl substrate for high yields, restricting the synthesis to ligands with simple bridging groups. Later, others showed that solvent-free condensation gives simple *bis*(pyrazolyl)alkanes in moderate yields from a 1:1 ratio of *bis*(pyrazolyl)methanone and carbonyl.[13] Alternatively, other contributors reported the *in situ* preparation and stoichiometric reaction of air-sensitive sulfinyldipyrazoles with carbonyls in good yields.[14] More recently, the sulfinyldipyrazole-based protocol has been applied to pyrazoles with 3-substituents larger than methyl.[15] This underexplored modification provides ligands with improved steric tuning and site isolation, which seeks to avoid deactivation by metal aggregation or homoleptic complex formation. Also of ongoing interest, variation of the coordinating groups' basicity and geometry promises improved electronic tuning within this ligand class. However, to our knowledge, this condensation approach has not been applied to heteroazoles other than pyrazoles and imidazoles. Furthermore, the involvement of air-sensitive reagents and intermediates, as well as residues of the transition-metal catalyst in the product, remain practical disadvantages of the existing condensation methods for *bis*(pyrazolyl)alkane synthesis.

In this report, we describe a new method for the synthesis of *bis*(pyrazolyl)alkanes based on the nucleophile-catalyzed condensation between carbonyls and *bis*(pyrazolyl)-

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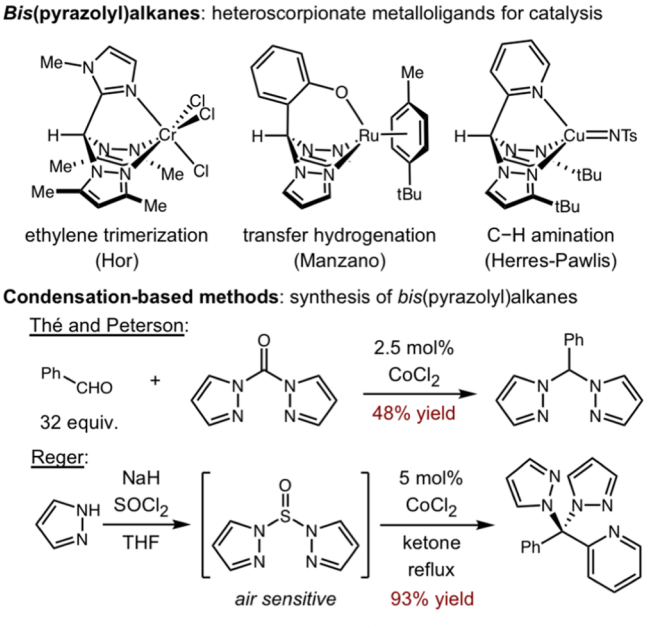
Scheme 1. Methods for Poly(pyrazolyl)alkane Synthesis



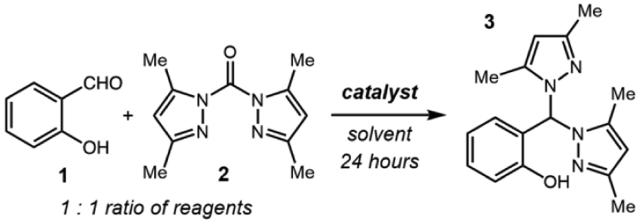
methanones (Scheme 1, bottom). The conditions are mild and avoid both metal catalysts and air-sensitive reagents. We show that this reaction accommodates both large 3-substituents on the pyrazole and an electronically diverse set of heterocycles in good to high yields using a 1:1 ratio of reagents. Finally, we characterize a two-cycle catalytic mechanism involving a carbamate intermediate, providing to our knowledge the most complete mechanism proposed for carbonyl/*bis*(pyrazolyl)methanone condensation.

RESULTS AND DISCUSSION

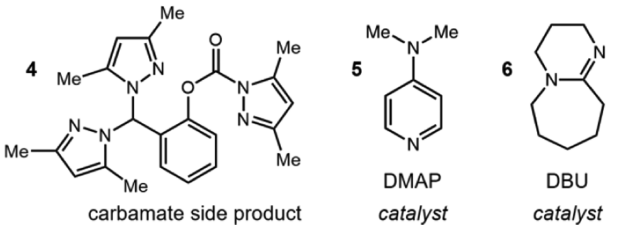
Originally, Thé and Peterson had proposed a carbamate intermediate formed through a metal-catalyzed acylation step for their catalytic condensation (see below).[16] Given the more recent development of nucleophilic catalysis for acylation,[17] we speculated that a related metal-free method would be possible using common nucleophiles instead. Along these lines, we evaluated catalytic quantities of common Lewis bases and acids to promote the 1:1 condensation of salicylaldehyde (**1**) and *bis*(3,5-dimethylpyrazol-1-yl)methanone (**2**) in toluene at 110 °C (Table S4.1). Under these conditions, in the absence of the catalyst, **3** was the minor product (27% yield, entry 1) and carbamate **4** was the major product (33% yield).[18] In contrast, several nucleophilic catalysts considerably improved the yield of **3** and selectivity over **4** (Table S4.1, entries 2–8), while the use of catalytic acids all resulted in lower yields compared with the catalyst-free control (entries 9–12).

We next evaluated several common solvents near their boiling point, ultimately identifying dry tetrahydrofuran (THF) at 60 °C as optimal. Under these conditions (Table 1), we found that 4-(*N*,*N*-dimethylamino)pyridine (DMAP)

Table 1. Catalyst Evaluation and Optimization[a]



entry	catalyst	loading (mol %)	solvent	yield[b] (%)
1	DMAP	10	THF	89
2	DBU	10	THF	80
3	quinuclidine	10	THF	85
4	potassium 2-pyridone	10	THF	85
5	TBD	10	THF	76
6	1-methylimidazole	10	THF	72
7	DABCO	10	THF	63
8	triphenylphosphine	10	THF	54
9	none		THF	31
10	DMAP	5	THF	38
11	DMAP	20	THF	59
12	DMAP	10	$CHCl_3$	28
13	DMAP	10	acetonitrile	54
14	DMAP	10	toluene	23
15	DMAP	10	DMF	52



[a]Reactions were perfomed using 1:1 ratio of **1**:**2** at 0.5 mmol of 1 in 3 mL of anhydrous THF at 60 °C, unless noted otherwise. [b]Yields obtained by crude ^{1}H NMR analysis with an internal standard.

(**5**) provided the highest yield of **3** (89%, entry 1). Nevertheless, the neutral, nitrogen-based nucleophiles 1,8-diazabicycloundec-7-ene (DBU) (**6**), quinuclidine, potassium 2-pyridone, and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) also performed well (entries 2–5), and we later found that DBU was the optimal catalyst for certain substrates. Yield of **3** was higher at 10 mol % catalyst loading than at 5 or 20 mol % (entries 10 and 11). Finally, higher yields were obtained in THF than in any of the common solvents such as toluene, acetonitrile, chloroform, and *N*,*N*-dimethylformamide at 60 °C (entries 12–15).

Having identified effective catalytic conditions, we next evaluated the synthesis of *bis*(azolyl)alkanes with 3-substituted pyrazoles and other heterocycles by reaction with aldehyde **1** (Table 2). To our knowledge, *bis*(azolyl)alkanes have only been prepared by condensation from pyrazoles, imidazole, and benzimidazole.[19] Promisingly, we could prepare all of the corresponding *bis*(azolyl)methanone precursors in high yield by acylation with triphosgene (Sections S1 and S2). Indeed, both sterically hindered and unhindered pyrazoles react successfully and in similar isolated yields (entries 1–6), promising for the synthesis of sterically varied ligand libraries. Among the other heterocycles, *bis*(azolyl)alkanes were obtained in good yields not only with simple imidazole and

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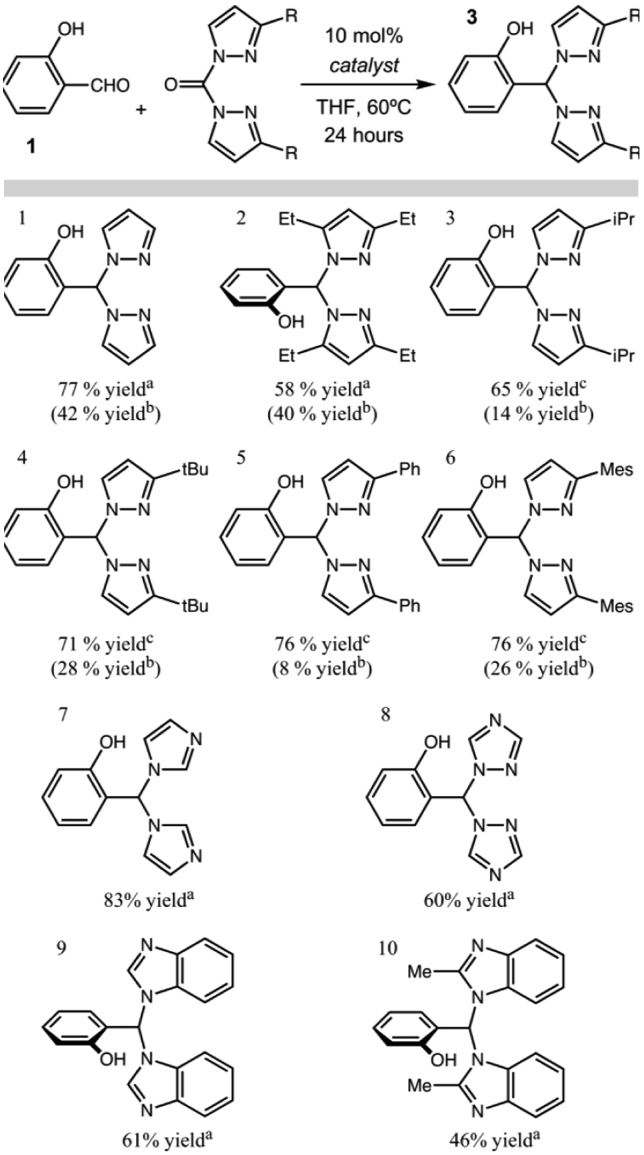
Table 2. Azole Scope under Catalytic Conditions[a]

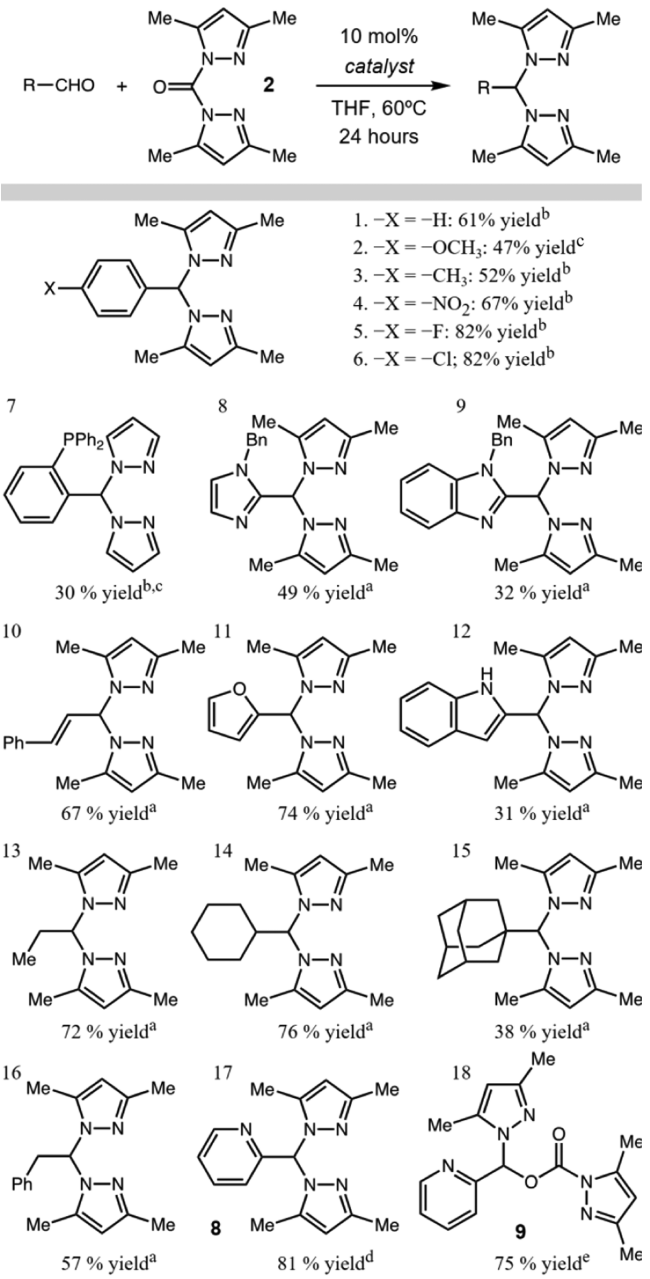


[a]Yields were obtained by isolation. [b]Performed with 10 mol % DBU. [c]Performed with no catalyst. [d]Performed with 10 mol % DMAP.

benzimidazole (entries 7 and 9) but also with 1,2,4-triazole and 2-methylimidazole (entries 8 & 10), heterocycles previously unreported for this reaction. The reaction with imidazole (entry 7) was scaled up to 10 mmol, resulting in an isolated yield of 80% after workup by simple filtration. The unsubstituted products are promising precursors for polytopic N-heterocyclic carbene ligands,[20] while the 2-substituted imidazoles highlight the success of this method toward sterically hindered substrates. In contrast, condensation with pyrrole- or indole-based precursors did not result in *bis*(pyrrolyl)alkanes. Presumably, nucleophilic catalysis requires a good pK_a match between the azolide leaving group and the nucleophile, as has been well studied for nucleophile-catalyzed acylation.[21] Notably, catalyst omission experiments show clear and consistent decreases in yields without the nucleophile for all of the azoles evaluated, confirming DMAP's role in the reaction.

We next evaluated the aldehyde scope of the nucleophile-catalyzed condensation using **2** as methanone. Under these conditions, we obtained moderate to good yields of the *bis*(pyrazolyl)alkane product for a range of phenyl, heteroaryl, and alkyl aldehydes (Table 3). The series of para-substituted benzaldehydes demonstrated the effectiveness of this method within a wide electronic range (entries 1−6). Similarly, we successfully prepared heteroscorpionate ligands with a range of coordinating groups using heteroaryl and 2-(diphenylphosphino)phenyl aldehydes, albeit in reduced yields

Table 3. Aldehyde Scope of Catalytic Condensation[a]



[a]All yields were obtained by isolation. [b]Performed with 10 mol % DMAP as the catalyst. [c]Performed with 10 mol % DBU. [d]*Bis*(pyrazolyl)methanone was used instead of *bis*(3,5-dimethylpyrazolyl)methanone. [e]Performed with no catalyst. [f]Performed at 22 °C with TBD as the catalyst.

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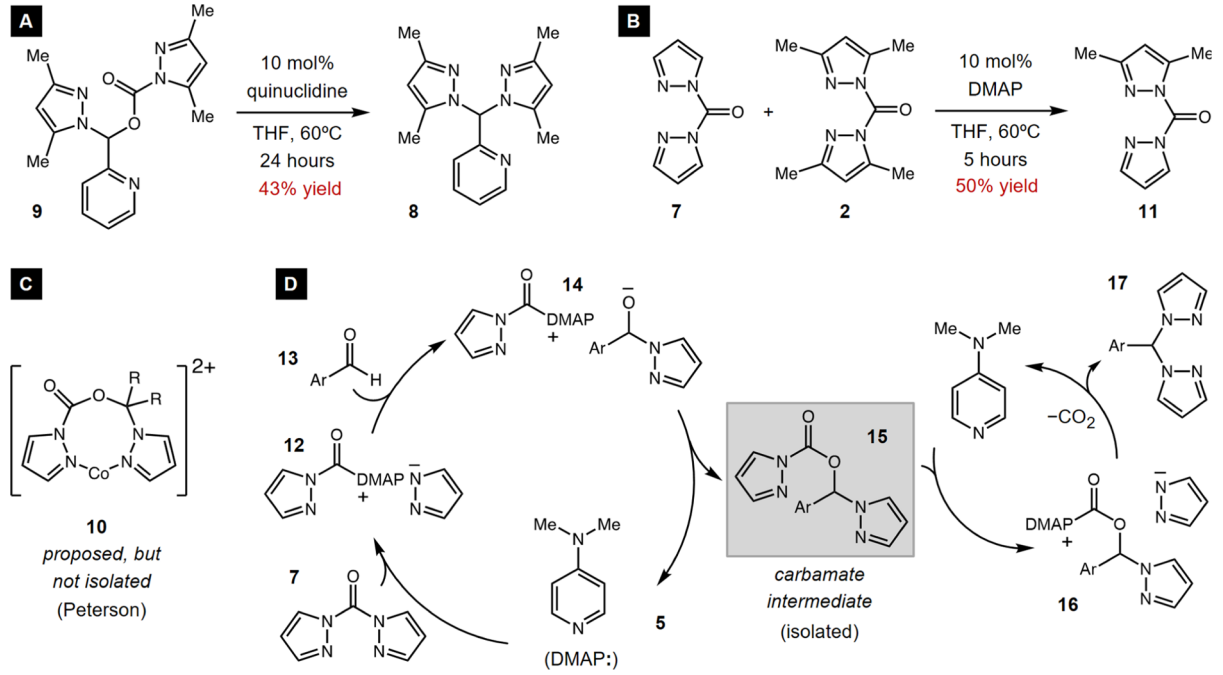
Scheme 2. (A) Intermediate Resubmission Experiment; (B) Crossover Experiment; (C) Carbamate Intermediate Proposed by Thé and Peterson;[16] (D) Proposed Bicyclic Mechanism for Nucleophile-Catalyzed Condensation of 1 and 2



for sterically hindered and electron-rich aldehydes (entries 7, 8, 9, 11, and 12). Furthermore, the protocol provides *bis*(pyrazolyl)alkanes bearing vinyl, primary alkyl, secondary alkyl, and tertiary alkyl substituents at the bridging carbon (entries 10 and 13−16), providing an additional handle for steric tuning and postsynthetic elaboration. For all of these substrates, **5** or **6** were optimal as catalysts. In contrast, although 2-formylpyridine was amenable to catalysis, we still obtained the highest yield with this substrate without the nucleophile in near-boiling toluene.

Fortuitously, under nucleophilic catalysis at ambient temperature with 2-formylpyridine, we obtained carbamate **9** as the major product in good yield (Table 3, entry 16). This product directly resembles the reaction intermediate **10** (Scheme 2C), proposed but not isolated by Thé and Peterson.[16] We did not find any analogous carbamate from a substructure search in SciFinder or Reaxys, however, and this key finding formed the basis of our mechanistic analysis of this reaction.

To confirm the role of this carbamate as an intermediate and not a byproduct, we first submitted **9** to a range of nucleophiles in THF at 60 °C (Scheme 2A). Indeed, carbamate **9** was converted to *bis*(pyrazolyl)alkane **8** in 43% yield with quinuclidine as the catalyst. Next, we sought to confirm whether the nucleophile adds reversibly to the *bis*(pyrazolyl)-methanone substrate as the first step in a nucleophile-catalyzed acylation mechanism. Because crossover between labeled *bis*(pyrazolyl)methanones would be predicted by this mechanism, we submitted **2** and **7** to nucleophilic catalysis with 10 mol % DMAP in THF at 60 °C. Consistently, after 5 h, we observed a statistical mixture of **2**, **7**, and crossover product **11** (Scheme 2B). Finally, we studied this reaction by Hammett analysis to distinguish between a charge-building aldehyde-activation step involving nucleophilic addition into the carbonyl and a charge-depleting step involving electrophilic acyl transfer. After performing a series of competition experiments between benzaldehyde and various 4-substituted benzaldehydes, we obtained a Hammett ρ value of +2.04 (Section S5) consistent with a selectivity-determining reaction of aldehyde with a nucleophile.

Based on these data, we propose a bicyclic catalytic mechanism linked by this carbamate intermediate (Scheme 2D). First, the addition of nucleophile **5** into *bis*(pyrazolyl)-methanone **7** generates ion pair **12** consisting of the acylated catalyst and pyrazolate, consistent with our crossover results. Then, selectivity-determining nucleophilic addition of the pyrazolate into aldehyde **13**, consistent with our Hammett analysis, would generate ion pair **14**. Then, acyl transfer would regenerate **5** and furnish carbamate **16**. In the second cycle, nucleophilic addition into **16** would generate ion pair **17**. Nucleophilic addition along with loss of CO_2 would then regenerate catalyst **5** and furnish the product.

Interestingly, analogous results but lower yields were obtained by these experiments in the absence of the catalyst: **9** was converted to **8** in 25% yield, **11** was formed from **2** and **7** in 33% yield, and a Hammett ρ value of +1.48 was obtained under identical conditions without the nucleophile. We interpret these results as evidence for an uncatalyzed background reaction by a similar mechanism, albeit in reduced selectivity and efficiency. Nevertheless, the fact that the catalyst improves the yield and selectivity not only on the overall reaction but also in both of these mechanistic experiments supports our claim of catalyst involvement in both the generation and conversion of carbamate **15**.

CONCLUSIONS

In summary, our nucleophile-catalyzed condensation of *bis*(azolyl)methanones and aldehydes provides a wide range of *bis*(azolyl)alkanes in good to high yields. The method avoids air-sensitive reagents, metal catalysts, reagent excess, and high reaction temperatures. Sterically hindered azole and aldehyde components both react efficiently, providing a modular handle

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for steric modification of metal−ligand complexes. Likewise, nucleophilic condensation accommodates aldehydes and azoles of varying electronics, from electron-rich to electron-poor. These substrates are directly applicable to the synthesis of polytopic N-heterocyclic carbenes and complex heteroscorpionate ligands. We anticipate that this method will enable the synthesis of more elaborate heteroscorpionate ligands for catalysis, featuring more readily tailored substitution, geometry, and electronics for catalyst fine-tuning.

EXPERIMENTAL SECTION

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[22] All solvents were purified according to the method of Grubbs.[23] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using force-flow chromatography on VWR silica gel according to the method of Still.[24] Thin-layer chromatography was performed on Merck 250 μm silica gel plates. Compounds were visualized by irradiation with UV light, treatment with a solution of potassium permanganate followed by heating, or exposure to iodine. Yields refer to pure compounds, unless otherwise indicated.

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL (400 MHz) spectrometer and are internally referenced relative to residual protio solvent signals ($CDCl_3$) at δ 7.27 ppm (^{1}H) or DMSO-d_6 at δ 2.50 ppm (^{1}H). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, and ap = apparent), integration, and coupling constant (Hz). ^{13}C spectra are referenced relative to $CDCl_3$ at δ 77.16 ppm or DMSO-d_6 at δ 39.52 ppm. Data for ^{13}C NMR are reported in terms of chemical shift and multiplicity where appropriate. IR spectra were recorded on a Thermo Fisher Nicolet iS10 spectrometer with a Smart iTR diamond plate and are reported in terms of wavenumber of absorption (cm^{-1}). High-resolution mass spectra were obtained from The University of Texas at Austin's Mass Spectrometry Facility.

Synthesis of Pyrazoles. *3,5-Diethyl-1H-pyrazole.* 3,5-Heptanedione (1.35 mL, 10.0 mmol, 1.0 equiv) was mixed with 10 mL of ethanol in a 50 mL round bottom flask, and hydrazine monohydrate (0.58 mL, 12 mmol, 1.2 equiv) was added to it at room temperature. After stirring overnight, all volatiles were removed under vacuum, giving the desired product as a yellow solid (1.16 g, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.68 (s, 1H), 5.89 (s, 1H), 2.67 (q, J = 7.6 Hz, 4H), 1.26 (t, J = 7.8 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 150.5, 100.7, 20.4, 13.8. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[25]

3-Isopropyl-1H-pyrazole. It was prepared according to a reported literature procedure.[26]

3-tert-Butyl-1H-pyrazole. It was prepared according to a reported literature procedure.[27]

3-Mesityl-1H-pyrazole. It was prepared by a modification to a reported literature procedure.[28] Potassium *tert*-butoxide (4.38 g, 39.1 mmol, 1.3 equiv) was added in one portion to a stirring solution of 2′,4′,6′-trimethylacetophenone (5.0 mL, 30 mmol, 1 equiv), ethyl formate (7.3 mL, 90 mmol, 3 equiv), and toluene (40 mL). Following a brief and mild exothermic reaction, the initially homogenous reaction became a yellow suspension. This mixture was stirred for another hour at room temperature and then partitioned between ethyl acetate and water, stirring until two homogeneous phases were observed. The mixture was acidified to pH 4 by the addition of acetic acid followed by extraction with ethyl acetate two times. The combined organic layer was washed with saturated aqueous $NaHCO_3$, and the resultant aqueous layer was extracted once more with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the intermediate mesityl α-hydroxymethyleneacetone as a yellow oil. The crude intermediate was dissolved in ethanol (40 mL), and then, hydrazine monohydrate (9.0 mL, 190 mmol) was added while stirring. This yellow solution was stirred for 2 h, and then ethanol was removed using a rotary evaporator. The leftover residue was extracted three times with dichloromethane. The combined organic layer was washed twice with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a red oil which crystallized upon standing. The crude product was recrystallized from boiling toluene to give an orange solid which was collected by vacuum filtration and washed with cold toluene until the orange color disappears, leaving behind the product as white crystals (2.49 g, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (s, 1H), 6.92 (s, 2H), 6.20 (s, 1H), 2.31 (s, 3H), 2.07 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.7, 138.4, 138.0, 136.8, 128.2, 128.1, 105.9, 21.2, 20.4. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[28]

General Procedure for *Bis*(pyrazolyl)methanones. An oven-dried Schlenk flask was charged with pyrazole, anhydrous THF, and triethylamine under nitrogen. The solution was allowed to stir for 30 min and then cooled to 0 °C. Triphosgene as a solution in anhydrous THF was added dropwise over 10 min. The resulting pale-yellow and inhomogeneous suspension was allowed to warm to room temperature and stir for 4 h. The reaction was then filtered, the solids were washed with THF, and the combined filtrate and washings were concentrated in vacuo to yield a pale yellow solid which was purified by recrystallization from the appropriate solvent or by column chromatography. *The bis(pyrazolyl)methanones slowly hydrolyze in air and should be stored cold or in a desiccator.*

Bis(pyrazol-1-yl)methanone. It was prepared by the general procedure with pyrazole (1.38 g, 20.2 mmol, 6 equiv), triethylamine (3.1 mL, 22 mmol, 6.5 equiv), triphosgene (1.0 g, 3.4 mmol, 1 equiv), and THF (75 mL). The crude product was recrystallized from dichloromethane/hexanes by first dissolving the crude product in boiling dichloromethane and then slowly adding boiling hexanes until the solution turns turbid, followed by a minimal amount of boiling dichloromethane until the solution just turns clear. After storage at −20 °C overnight, the product was isolated as a white solid (1.27 g, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, J = 2.7 Hz, 2H), 7.87 (s, 2H), 6.52 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.5, 144.6, 134.2, 110.0. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[29]

Bis(3,5-dimethylpyrazol-1-yl)methanone (2). It was prepared by the general procedure with 3,5-dimethylpyrazole (19.4 g, 202 mmol, 6 equiv), triethylamine (30.5 mL, 219 mmol, 6.5 equiv), triphosgene (10 g, 34 mmol, 1 equiv), and THF (300 mL). The crude product was recrystallized from dichloromethane/hexanes by first dissolving the crude product in boiling dichloromethane and then slowly adding boiling hexanes until the solution turns turbid, followed by a minimal amount of boiling dichloromethane until the solution just turns clear. After storage at −20 °C overnight, the product was isolated as an ecru solid (19.12 g, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03 (s, 2H), 2.46 (s, 6H), 2.26 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 153.1, 148.0, 145.5, 111.5, 14.1, 13.2. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[29]

Bis(3,5-diethylpyrazol-1-yl)methanone. It was prepared by the general procedure with 3,5-diethylpyrazole (1.16 g, 9.33 mmol, 6 equiv), triethylamine (1.41 mL, 10.1 mmol, 6.5 equiv), triphosgene (0.460 g, 1.55 mmol, 1.0 equiv), and THF (50 mL). The crude product was recrystallized from hexanes to give a brown solid (1.20 g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (s, 1H), 2.80 (q, J = 7.4 Hz, 2H), 2.58 (q, J = 7.6 Hz, 2H), 1.14−1.21 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.3, 151.5, 148.2, 107.9, 21.7, 20.5, 13.2, 12.7. HRMS (ESI-TOF) m/z: $[M + H]^+$, calcd for $C_{15}H_{23}N_4O$, 275.1866; found, 275.1868, difference −0.75 ppm.

Bis(3-isopropylpyrazol-1-yl)methanone. It was prepared by the general procedure with 3-isopropylpyrazole (2.23 g, 20.2 mmol, 6 equiv), triethylamine (3.1 mL, 22 mmol, 6.5 equiv), triphosgene (1.0 g, 3.4 mmol, 1 equiv), and THF (50 mL). The crude product was purified by flash chromatography on silica using 8:1 hexanes/ethyl acetate to give a colorless oil (2.44 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (s, 2H), 6.36 (s, 2H), 3.03−3.13 (m, 2H), 1.29 (d, J = 6.7 Hz, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 164.9, 134.8,

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107.8, 28.2, 22.7, 22.1. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[30]

Bis(3-tert-butylpyrazol-1-yl)methanone. It was prepared by the general procedure with pyrazole (2.51 g, 20.1 mmol, 6 equiv), triethylamine (3.1 mL, 22 mmol, 6.5 equiv), triphosgene (1.0 g, 3.4 mmol, 1 equiv), and THF (50 mL). The crude product was recrystallized by dissolving in boiling hexanes and then storing at −20 °C overnight to obtain the product as an ecru solid (2.01 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, J = 2.7 Hz, 2H), 6.40 (d, J = 2.5 Hz, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.5, 144.7, 134.7, 107.5, 30.5, 29.9. HRMS (ESI-TOF) m/z: $[M + H]^+$, calcd for $C_{15}H_{23}N_4O$, 275.1866; found, 275.1868, difference −0.53 ppm.

Bis(3-phenylpyrazol-1-yl)methanone. It was prepared by the general procedure with 3-phenylpyrazole (2.91 g, 20.2 mmol, 6 equiv), triethylamine (3.1 mL, 22 mmol, 6.5 equiv), triphosgene (1.0 g, 3.4 mmol, 1 equiv), and THF (100 mL). The crude product was recrystallized by dissolving in boiling THF and then storing at −20 °C overnight to obtain the product as a white solid (2.36 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (d, J = 1.4 Hz, 2H), 7.95 (d, J = 7.5 Hz, 4H), 7.41−7.49 (m, 6H), 6.89 (d, J = 1.4 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.8, 144.5, 135.7, 131.3, 129.8, 129.0, 126.8, 107.9. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[31]

Bis(3-mesitylpyrazol-1-yl)methanone. It was prepared by the general procedure with 3-mesitylpyrazole (1.36 g, 7.30 mmol, 6 equiv), triethylamine (1.1 mL, 7.9 mmol, 6.5 equiv), triphosgene (0.36 g, 1.2 mmol, 1 equiv), and THF (20 mL). The crude product was purified by flash chromatography on silica using 4:1 hexanes/ethyl acetate to give a white solid (1.16 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (d, J = 2.7 Hz, 2H), 6.94 (s, 4H), 6.45 (d, J = 2.5 Hz, 2H), 2.32 (s, 6H), 2.16 (s, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.0, 144.5, 138.6, 137.3, 134.9, 129.0, 128.4, 111.9, 21.3, 20.6. HRMS (ESI-TOF) m/z: $[M + H]^+$, calcd for $C_{25}H_{27}N_4O$, 399.2179; found, 399.2181, difference −0.50 ppm.

General Procedure for *Bis*(imidazolyl)methanones. An oven-dried Schlenk flask was charged with triphosgene and anhydrous THF under nitrogen. The solution was then cooled to 0 °C, and a solution of imidazole in anhydrous THF was added to it via a syringe. The reaction mixture was stirred for 24 h, and white crystalline imidazole hydrochloride was removed by filtration, and the filtrate was concentrated down on a rotary evaporator, resulting in a white powder.

Bis(benzimidazol-1-yl)methanone. It was prepared by the general procedure with 1,3-benzodiazole (1.47 g, 12.5 mmol, 12.5 equiv), triphosgene (0.30 g, 1.0 mmol, 1.0 equiv), and THF (50 mL). The crude product was recrystallized from hexanes to give a white solid (0.754 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 2H), 7.89 (d, J = 17.7 Hz, 4H), 7.49 (t, J = 3.1 Hz, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.9, 144.0, 141.3, 131.9, 126.4, 126.0, 121.5, 114.2. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[32]

Bis(2-methylbenzimidazol-1-yl)methanone. It was prepared by the general procedure with 2-methylbenzimidazole (1.65 g, 12.5 mmol, 12.5 equiv), triphosgene (0.30 g, 1.0 mmol, 1.0 equiv), and THF (50 mL). The crude product was recrystallized from hexanes to give a white solid (820 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 7.8 Hz, 2H), 6.92 (t, J = 7.7 Hz, 2H), 6.73 (t, J = 7.7 Hz, 2H), 6.31 (d, J = 8.2 Hz, 2H), 2.31 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.1, 146.9, 142.4, 132.3, 125.1, 125.0, 120.2, 112.2, 16.1. HRMS (ESI-TOF) m/z: $[M + H]^+$, calcd for $C_{17}H_{15}N_4O$, 291.1240; found, 291.1244, difference −1.38 ppm.

General Procedure for Nucleophile-Catalyzed Condensation. *Bis*(pyrazolyl)methanone or *bis*(imidazolyl)methanone was dissolved in THF with the aldehyde and catalyst. The headspace of the vial or flask was purged with nitrogen. The reaction mixture was stirred at 60 °C using an aluminum block for 24 h. After cooling down to room temperature, all volatiles were removed under vacuum and the reactants were purified by flash chromatography or other methods.

*2-Bis(3,5-dimethylpyrazol-1-yl)methylphenol (**3**).* The product was prepared according to the general procedure with salicylaldehyde (**1**, 0.104 mL, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (**2**, 218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.10 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 3:1 hexanes/ethyl acetate to obtain the product as a white solid (251 mg, 85% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.86 (s, 1H), 7.58 (s, 1H), 7.18 (t, J = 7.5 Hz, 1H), 6.83 (t, J = 9.0 Hz, 2H), 6.76 (t, J = 7.5 Hz, 1H), 5.87 (s, 2H), 2.07 (s, 6H), 2.04 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 154.5, 146.3, 139.4, 129.7, 128.7, 122.8, 118.7, 115.1, 106.1, 68.4, 13.5, 10.8. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[29]

2-Bis(pyrazol-1-yl)methylphenol (Table 2, Entry 1). The product was prepared according to the general procedure with salicylaldehyde (0.104 mL, 1.00 mmol, 1.0 equiv), *bis*(pyrazol-1-yl)methanone (162 mg, 1.00 mmol, 1.0 equiv), DBU (15.2 μL, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 3:1 hexanes/ethyl acetate to obtain the product as a white solid (184 mg, 77% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.07 (s, 1H), 7.96 (s, 1H), 7.67 (s, 2H), 7.56 (s, 2H), 7.24 (t, J = 7.6 Hz, 1H), 6.89 (t, J = 8.3 Hz, 2H), 6.80 (t, J = 7.5 Hz, 1H), 6.32 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 154.7, 139.9, 130.4, 129.9, 127.8, 122.6, 118.9, 115.5, 105.8, 72.3. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[33]

2-Bis(3,5-diethylpyrazol-1-yl)methylphenol (Table 2, Entry 2). The product was prepared according to the general procedure with salicylaldehyde (0.104 mL, 1.00 mmol, 1.0 equiv), *bis*(3,5-diethylpyrazol-1-yl)methanone (274 mg, 1.00 mmol, 1.0 equiv), DBU (15.2 μL, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography using 10:1 hexanes/ethyl acetate to obtain the product as a white solid (205 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.31 (s, 1H), 7.51 (s, 1H), 7.06 (t, J = 7.2 Hz, 1H), 6.87 (d, J = 6.7 Hz, 1H), 6.68−6.80 (m, J = 7.8 Hz, 2H), 5.91 (s, 2H), 2.56 (q, J = 7.4 Hz, 4H), 2.46 (q, J = 7.2 Hz, 4H), 1.17 (t, J = 7.5 Hz, 6H), 1.10 (t, J = 7.3 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.4, 154.0, 146.7, 130.3, 129.2, 122.5, 119.3, 117.8, 103.2, 72.4, 21.5, 18.8, 13.8, 12.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$, calcd for $C_{21}H_{28}N_4ONa$, 375.2155; found, 375.2155, difference 0.14 ppm.

2-Bis(3-isopropylpyrazol-1-yl)methylphenol (Table 2, Entry 3). The product was prepared according to the general procedure with salicylaldehyde (0.104 mL, 1.00 mmol, 1.0 equiv), *bis*(3-isopropylpyrazol-1-yl)methanone (246 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.10 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 9:1−6:1 hexanes/ethyl acetate to obtain the product as a white solid (210 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.73 (s, 1H), 7.63 (s, 1H), 7.40 (s, 2H), 7.09 (t, J = 7.7 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.71−6.77 (m, 2H), 6.07 (s, 2H), 2.92−3.02 (m, 2H), 1.23 (d, J = 7.1 Hz, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 160.3, 155.5, 131.5, 130.7, 130.4, 121.7, 119.8, 119.2, 103.1, 77.4, 27.8, 22.7. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[33]

2-Bis(3-tert-butylpyrazol-1-yl)methylphenol (Table 2, Entry 4). The product was prepared according to the general procedure with salicylaldehyde (0.104 mL, 1.00 mmol, 1.0 equiv), *bis*(3-*tert*-butylpyrazol-1-yl)methanone (274 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.10 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 5−10% ethyl acetate in hexanes to obtain the product as a white solid (249 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 2H), 7.31−7.35 (m, 2H), 7.08 (d, J = 7.9 Hz, 1H), 6.88 (t, J = 7.5 Hz, 1H), 6.09 (s, 2H), 1.25 (s, 18H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 163.1, 155.7, 131.3, 130.5, 130.1, 121.9, 119.5, 118.6, 102.6, 77.5, 77.2, 76.9, 32.3, 30.6. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[33]

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2-Bis(3-phenylpyrazol-1-yl)methylphenol (Table 2, Entry 5). The product was prepared according to the general procedure with salicylaldehyde (0.104 mL, 1.00 mmol, 1.0 equiv), *bis*(3-phenylpyrazol-1-yl)methanone (314 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.10 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 3:1 hexanes/ethyl acetate to obtain the product as a white solid (299 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.88 (s, 1H), 7.74−7.77 (m, 6H), 7.62 (s, 1H), 7.37 (t, J = 7.3 Hz, 4H), 7.19−7.32 (m, 4H), 6.95 (d, J = 8.0 Hz, 1H), 6.87 (t, J = 7.2 Hz, 1H), 6.59 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.5, 152.8, 132.4, 132.2, 132.0, 131.0, 128.8, 128.4, 126.0, 121.0, 120.3, 119.8, 103.8, 78.7. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[33]

2-Bis(3-mesitylpyrazol-1-yl)methyl-phenol (Table 2, Entry 6). The product was prepared according to the general procedure with salicylaldehyde (0.104 mL, 1.00 mmol, 1.0 equiv), *bis*(3-mesitylpyrazol-1-yl)methanone (399 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.10 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 6:1 hexanes/ethyl acetate to obtain the product as a white solid (363 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 1.8 Hz, 2H), 7.37−7.45 (m, 3H), 7.25 (s, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.96 (t, J = 7.7 Hz, 1H), 6.87 (s, 4H), 6.16 (d, J = 2.1 Hz, 2H), 2.28 (s, 6H), 1.99 (s, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.9, 152.0, 137.9, 137.5, 132.2, 131.8, 131.1, 129.9, 128.2, 120.6, 120.4, 120.1, 107.4, 79.4, 21.2, 20.5. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[33]

2-Bis(imidazol-1-yl)methylphenol (Table 2, Entry 7). The product was prepared according to the general procedure with salicylaldehyde (0.104 mL, 1.00 mmol, 1.0 equiv), 1,1′-carbonyldiimidazole (162 mg, 1.00 mmol, 1.0 equiv), DBU (15.2 μL, 0.100 mmol, 0.1 equiv), and THF (3 mL). The product precipitated out from the reaction mixture and was collected by filtration, resulting in a white solid (198 mg, 83% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.24 (s, 1H), 7.92 (s, 1H), 7.70 (s, 2H), 7.23 (t, J = 7.6 Hz, 1H), 7.18 (s, 2H), 6.95 (s, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.80 (t, J = 7.2 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 155.2, 137.4, 131.3, 129.5, 127.2, 123.0, 119.7, 119.1, 116.2, 65.6. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[34]

2-Bis(imidazol-1-yl)methylphenol (10 mmol Scale) (Table 2, Entry 7). The product was prepared according to the general procedure with salicylaldehyde (1.04 mL, 10.0 mmol, 1.0 equiv), 1,1′-carbonyldiimidazole (1.62 g, 10.0 mmol, 1.0 equiv), DBU (15.2 μL, 0.100 mmol, 0.1 equiv), and THF (30 mL). The product precipitated out from the reaction mixture and was collected by filtration and washed with acetone, resulting in a white solid (1.91 g, 80% yield).

2-Bis(1,2,4-triazol-1-yl)methyl-phenol (Table 2, Entry 8). The product was prepared according to the general procedure with salicylaldehyde (0.104 mL, 1.00 mmol, 1.0 equiv), 1,1′-carbonyldi-(1,2,4-triazole) (164 mg, 1.00 mmol, 1.0 equiv), DBU (15.2 μL, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 10% methanol in dichloromethane to obtain the product as a yellow crystalline solid (146 mg, 60% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.27 (s, 1H), 8.63 (s, 2H), 8.25 (s, 1H), 8.07 (s, 2H), 7.27 (t, J = 7.7 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.83 (t, J = 7.4 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 155.3, 152.8, 145.1, 131.7, 128.4, 120.6, 119.8, 116.1, 68.7, 40.6, 40.4, 40.2, 40.0, 39.8, 39.6, 39.4. HRMS (ESI-TOF) m/z: [M + Na]$^+$, calcd for $C_{11}H_{10}N_6ONa$, 265.0808; found, 265.0815, difference −2.45 ppm.

2-Bis(benzimidazol-1-yl)methylphenol (Table 2, Entry 9). The product was prepared according to the general procedure with salicylaldehyde (0.104 mL, 1.00 mmol, 1.0 equiv), *bis*(benzimidazol-1-yl)methanone (262 mg, 1.00 mmol, 1.0 equiv), DBU (15.2 μL, 0.100 mmol, 0.1 equiv), and THF (3 mL). The product precipitated out from the reaction mixture and was collected by filtration, resulting in a white solid (208 mg, 61% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.37 (s, 1H), 8.46 (s, 1H), 8.26 (s, 2H), 7.72 (d, J = 7.6 Hz, 2H), 7.32 (d, J = 7.6 Hz, 3H), 7.16−7.24 (m, 4H), 7.02 (d, J = 7.9 Hz, 1H), 6.83 (t, J = 7.5 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 155.8, 144.2, 143.5, 143.3, 133.4, 131.9, 127.8, 123.8, 123.0, 120.6, 120.5, 119.8, 116.6, 111.3. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[35]

2-Bis(2-methyl-benzimidazol-1-yl)methylphenol (Table 2, Entry 10). The product was prepared according to the general procedure with salicylaldehyde (0.104 mL, 1.00 mmol, 1.0 equiv), *bis*(2-methyl-benzimidazol-1-yl)methanone (262 mg, 1.00 mmol, 1.0 equiv), DBU (15.2 μL, 0.100 mmol, 0.1 equiv), and THF (3 mL). The product was recrystallized from cold acetone and hexane, resulting in a white solid (169 mg, 46% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.25 (s, 1H), 7.99 (s, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.09 (b, 2H), 6.90−6.95 (m, 2H), 6.82 (t, J = 7.3 Hz, 2H), 6.44 (d, J = 7.6 Hz, 1H), 6.25 (d, J = 7.9 Hz, 2H), 2.04 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 156.1, 153.0, 152.0, 142.9, 135.6, 132.2, 127.4, 123.0, 120.3, 120.0, 119.7, 116.7, 111.0, 110.6, 14.9. HRMS (ESI-TOF) m/z: [M + Na]$^+$, calcd for $C_{23}H_{20}N_4ONa$, 391.1529; found, 391.1536, difference −1.70 ppm.

Bis(3,5-dimethylpyrazol-1-yl)methylbenzene (Table 3, Entry 1). The product was prepared according to the general procedure with benzaldehyde (0.102 mL, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.10 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 4:1 hexanes/ethyl acetate to obtain the product as a white solid (170 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.31 (s, 3H), 6.90 (d, J = 4.3 Hz, 2H), 5.85 (s, 2H), 2.21 (s, 6H), 2.19 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 148.4, 141.2, 136.9, 128.6, 128.5, 126.9, 106.9, 74.0, 13.9, 12.0. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[36]

1-Bis(3,5-dimethylpyrazol-1-yl)methyl-4-methoxybenzene (Table 3, Entry 2). The product was prepared according to the general procedure with 4-methoxybenzaldehyde (0.122 mL, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DBU (15.2 μL, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 9:1 hexanes/ethyl acetate to obtain the product as a colorless oil (147 mg, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1H), 6.83 (s, 4H), 5.83 (s, 2H), 3.77 (s, 3H), 2.19 (s, 6H), 2.18 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.6, 148.3, 141.1, 128.9, 128.2, 113.9, 106.9, 73.8, 55.3, 13.6, 11.9. HRMS (ESI-TOF) m/z: [M + Na]$^+$, calcd for $C_{18}H_{22}N_4ONa$, 333.1686; found, 333.1690, difference −1.12 ppm.

1-Bis(3,5-dimethylpyrazol-1-yl)methyl-4-methylbenzene (Table 3, Entry 3). The product was prepared according to the general procedure with 4-methylbenzaldehyde (0.118 mL, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.10 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 9:1−4:1 hexanes/ethyl acetate to obtain the product as a white solid (154 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.12 (d, J = 7.8 Hz, 2H), 6.80 (d, J = 7.8 Hz, 2H), 5.84 (s, 2H), 2.33 (s, 3H), 2.21 (s, 6H), 2.19 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 148.3, 141.1, 138.3, 133.9, 129.3, 126.8, 106.9, 74.0, 21.2, 13.9, 12.0. HRMS (ESI-TOF) m/z: [M + Na]$^+$, calcd for $C_{18}H_{22}N_4Na$, 317.1737; found, 317.1741, difference −1.36 ppm.

4-Bis(3,5-dimethylpyrazol-1-yl)methyl-nitrobenzene (Table 3, Entry 4). The product was prepared according to the general procedure with *p*-nitrobenzaldehyde (151 mg, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.10 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 3:1 hexanes/ethyl acetate to obtain the product as a yellow solid (218 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 8.9 Hz, 2H), 7.62 (s, 1H), 7.11 (d, J = 8.3 Hz, 2H), 5.88 (s, 2H), 2.19 (s, 6H), 2.18 (s,

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6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 149.0, 147.9, 143.8, 141.1, 128.3, 123.8, 107.5, 73.2, 13.8, 11.8. HRMS (ESI-TOF) m/z: $[M + H]^+$, calcd for $C_{17}H_{20}N_5O_2$, 326.1612; found, 326.1612, difference −0.29 ppm.

4-Bis(3,5-dimethylpyrazol-1-yl)methyl-fluorobenzene (Table 3, Entry 5). The product was prepared according to the general procedure for the preparation of *bis*(pyrazolyl)alkanes with 4-fluorobenzaldehyde (0.107 mL, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.10 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 5:1 hexanes/ethyl acetate to obtain the product as a white solid (245 mg, 82% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.01 (t, J = 8.6 Hz, 2H), 6.89−6.92 (m, 2H), 5.94−5.74 (2H), 2.20 (d, J = 6.2 Hz, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 148.6, 141.1, 128.9, 128.8, 115.7, 115.5, 107.1, 73.5, 13.8, 11.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −113.59. HRMS (ESI-TOF) m/z: $[M + Na]^+$, calcd for $C_{17}H_{19}FN_4Na$, 321.1486; found, 321.1489, difference −0.84 ppm.

4-Bis(3,5-dimethylpyrazol-1-yl)methyl-chlorobenzene (Table 3, Entry 6). The product was prepared according to the general procedure with 4-chlorobenzaldehyde (141 mg, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.10 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 10:1 hexanes/ethyl acetate to obtain the product as a white solid (259 mg, 82% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.29 (d, J = 8.3 Hz, 2H), 6.85 (d, J = 7.6 Hz, 2H), 5.85 (s, 2H), 2.19 (s, 6H), 2.18 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.6, 141.1, 135.4, 134.5, 128.8, 128.5, 107.1, 73.5, 13.8, 11.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$, calcd for $C_{17}H_{19}ClN_4Na$, 337.1190; found, 337.1194, difference −1.10 ppm.

2-Bis(pyrazol-1-yl)methyl-1-(diphenylphosphino)benzene (Table 3, Entry 7). The product was prepared according to the general procedure with 2-(diphenylphosphino)benzaldehyde (290 mg, 1.00 mmol, 1.0 equiv), *bis*(pyrazol-1-yl)methanone (162 mg, 1.00 mmol, 1.0 equiv), DBU (15.2 μL, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 2:1 hexanes/ethyl acetate to obtain the product as a white solid (121 mg, 30% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.58 (d, J = 7.5 Hz, 1H), 7.47 (s, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.21−7.32 (m, 7H), 7.18 (d, J = 2.3 Hz, 2H), 7.06−7.12 (m, 5H), 6.94 (dd, J = 7.3, 4.3 Hz, 1H), 6.08 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 140.9, 140.8 (d, J = 23.1 Hz), 136.4 (d, J = 18.3 Hz), 135.3 (d, J = 7.7 Hz), 135.0, 133.9 (d, J = 19.3 Hz), 129.9, 129.7, 129.5, 128.8, 128.5 (d, J = 7.7 Hz), 127.5 (d, J = 5.8 Hz), 106.3, 75.7 (d, J = 28.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ −18.04. HRMS (ESI-TOF) m/z: $[M + H]^+$, calcd for $C_{25}H_{22}N_4P$, 409.1577; found, 409.1576, difference 0.05 ppm.

N-Benzyl-2-bis(3,5-dimethylpyrazol-1-yl)methylimidazole (Table 3, Entry 8). The product was prepared according to the general procedure with *N*-benzyl-2-formylimidazole (186 mg, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using ethyl acetate to obtain the product mixed with pyrazole, which was then sublimed off at 80 °C, and the desired product was obtained as a pale yellow solid (186 mg, 49% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 4H), 7.07 (s, 1H), 6.99 (d, J = 5.8 Hz, 2H), 6.90 (s, 1H), 5.84 (s, 2H), 4.74 (s, 2H), 2.16 (s, 6H), 2.01 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 148.3, 141.3, 141.2, 135.5, 129.0, 128.3, 128.1, 127.6, 122.6, 107.6, 70.1, 50.5, 13.8, 11.3. HRMS (ESI-TOF) m/z: $[M + H]^+$, calcd for $C_{21}H_{25}N_6$, 361.2135; found, 361.2137, difference −0.42 ppm.

2-Bis(3,5-dimethylpyrazol-1-yl)methyl-N-benzyl-benzimidazole (Table 3, Entry 9). The product was prepared according to the general procedure with 2-formyl-*N*-benzylbenzimidazole (0.107 mL, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 5:1 hexanes/ethyl acetate to obtain the product as a white solid (131 mg, 32% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (t, J = 3.4 Hz, 1H), 7.48 (s, 1H), 7.19−7.31 (m, 6H), 6.92 (t, 2H), 5.85 (s, 2H), 5.03 (s, 2H), 2.13 (s, 6H), 2.07 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 148.6, 147.7, 141.4, 136.8, 135.6, 128.9, 128.0, 126.6, 123.7, 122.4, 121.0, 110.1, 107.7, 13.7, 11.5. HRMS (ESI-TOF) m/z: $[M + H]^+$, calcd for $C_{25}H_{27}N_6$, 411.2292; found, 411.2293, difference −0.35 ppm.

(E)-3,3-Bis(3,5-dimethylpyrazol-1-yl)-1-phenylpropene (Table 3, Entry 10). The product was prepared according to the general procedure with *trans*-cinnamaldehyde (0.126 mL, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 10:1 hexanes/ethyl acetate to obtain the product as a white solid (202 mg, 67% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 7.3 Hz, 2H), 7.20−7.32 (m, 3H), 7.05 (d, J = 21.4 Hz, 2H), 6.41 (d, J = 14.7 Hz, 1H), 5.82 (s, 2H), 2.22 (s, 6H), 2.20 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 147.9, 140.1, 135.9, 133.5, 128.6, 128.4, 127.2, 123.9, 107.1, 73.8, 13.8, 11.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$, calcd for $C_{19}H_{22}N_4Na$, 329.1737; found, 329.1740, difference −1.07 ppm.

1,1′-(Furan-2-ylmethylene)bis(3,5-dimethylpyrazole) (Table 3, Entry 11). The product was prepared according to the general procedure with 2-formylfuran (0.107 mL, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 5:1 hexanes/ethyl acetate to obtain the product as a white solid (200 mg, 74% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.45 (s, 1H), 6.38 (s, 1H), 6.22 (s, 1H), 5.83 (s, 2H), 2.21 (d, J = 7.6 Hz, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 148.6, 148.4, 143.2, 140.9, 110.9, 110.8, 107.1, 69.3, 13.9, 11.3. Our ^1H and ^{13}C NMR are consistent with those reported for this compound.[37]

Indole-2-bis(3,5-dimethylpyrazol-1-yl)methane (Table 3, Entry 12). The product was prepared according to the general procedure with indole-2-carboxaldehyde (145 mg, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 4:1 hexanes/ethyl acetate to obtain the product as a white solid (100 mg, 31% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 9.92 (s, 1H), 7.72 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.47 (s, 1H), 5.80 (s, 2H), 2.24 (s, 6H), 2.19 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 148.8, 140.8, 136.2, 132.4, 127.8, 122.6, 121.0, 120.0, 111.7, 107.1, 103.1, 68.3, 13.8, 11.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$, calcd for $C_{19}H_{21}N_5Na$, 342.1689; found, 342.1692, difference −0.92 ppm.

1,1-Bis(3,5-dimethylpyrazol-1-yl)propane (Table 3, Entry 13). The product was prepared according to the general procedure with propionaldehyde (0.072 mL, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 9:1 hexanes/ethyl acetate to obtain the product as a white solid (168 mg, 72% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 6.12 (t, J = 7.7 Hz, 1H), 5.73 (s, 2H), 2.53−2.61 (m, 2H), 2.16 (s, 6H), 2.15 (s, 6H), 0.88 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 147.3, 139.8, 106.8, 74.5, 26.4, 13.6, 11.2, 10.4. HRMS (ESI-TOF) m/z: $[M + H]^+$, calcd for $C_{13}H_{21}N_4$, 233.1761; found, 233.1769, difference −3.34 ppm.

Bis(3-phenylpyrazol-1-yl)cyclohexylmethane (Table 3, Entry 14). The product was prepared according to the general procedure with cyclohexanecarboxaldehyde (0.112 mL, 1.00 mmol, 1.0 equiv), *bis*(3-

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phenylpyrazol-1-yl)methanone (314 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 10:1 hexanes/ethyl acetate to obtain the product as a white solid (218 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (d, J = 11.0 Hz, 1H), 5.73 (s, 2H), 3.00 (q, J = 11.2 Hz, 1H), 2.34 (s, 6H), 2.17 (s, 6H), 1.67 (d, J = 10.4 Hz, 3H), 1.09−1.38 (m, 5H), 0.87−0.95 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 147.6, 139.9, 106.3, 76.7, 39.6, 29.5, 26.3, 25.5, 13.7, 11.5. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[38]

1-Bis(3,5-dimethylpyrazol-1-yl)methyladamantane (Table 3, Entry 15). The product was prepared according to the general procedure with 1-admantanal (164 mg, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 9:1 hexanes/ethyl acetate to obtain the product as a white solid (130 mg, 38% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72 (s, 2H), 5.61 (s, 1H), 2.19 (d, J = 12.3 Hz, 12H), 1.96 (s, 3H), 1.83 (s, 6H), 1.63 (t, J = 14.3 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 147.4, 139.9, 105.6, 77.2, 40.6, 39.0, 36.8, 28.4, 14.0, 11.9. HRMS (ESI-TOF) m/z: [M + H]$^+$, calcd for $C_{21}H_{31}N_4$, 339.2543; found, 339.2546, difference −0.76 ppm.

1-Phenyl-2,2-bis(3,5-dimethylpyrazol-1-yl)ethane (Table 3, Entry 16). The product was prepared according to the general procedure with freshly distilled phenylacetaldehyde (0.111 mL mg, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), DMAP (12.2 mg, 0.100 mmol, 0.1 equiv), and THF (3 mL). Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 6:1 hexanes/ethyl acetate to obtain the product as a white solid (168 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17−7.18 (m, 3H), 6.95−6.97 (m, 2H), 6.21 (t, J = 7.2 Hz, 1H), 5.72 (s, 2H), 3.89 (d, J = 7.1 Hz, 2H), 2.21 (s, 6H), 2.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.0, 139.6, 136.7, 129.4, 128.5, 127.0, 106.4, 72.3, 40.1, 13.8, 11.1. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[39]

2-Bis(3,5-dimethylpyrazol-1-yl)methylpyridine (8, Table 3, Entry 17). The product was prepared according to a modification of the general procedure with 2-formylpyridine (0.096 mL, 1.00 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (218 mg, 1.00 mmol, 1.0 equiv), and toluene (3 mL). The reaction mixture was stirred at 110 °C for 24 h. Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using 2:1−3:1 ethyl acetate/hexanes to obtain the product as an off-white solid (227 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, J = 4.1 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.55 (s, 1H), 7.22−7.24 (m, 1H), 6.91 (d, J = 8.0 Hz, 1H), 5.86 (s, 2H), 2.18 (s, 6H), 2.16 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.7, 149.6, 148.7, 140.8, 137.0, 123.3, 122.4, 107.0, 74.7, 13.9, 11.5. Our ^{1}H and ^{13}C NMR are consistent with those reported for this compound.[36]

1-(3,5-Dimethylpyrazol-1-yl)-(2-pyridinyl)methyl-3,5-dimethylpyrazole-carboxylate (9, Table 3, Entry 18). The product was prepared according to a modification of the general procedure with 2-formylpyridine (0.44 mL, 4.6 mmol, 1.0 equiv), *bis*(3,5-dimethylpyrazol-1-yl)methanone (1.0 g, 4.6 mmol, 1.0 equiv), TBD (52 mg, 0.46 mmol, 0.1 equiv), and dichloromethane (10 mL). The reaction mixture was stirred at 22 °C for 24 h. Volatiles were removed in vacuo, and then, the remaining residue was purified by flash chromatography on silica using ethyl acetate to obtain the product as a light tan solid mixed with pyrazole. This was suspended in hexanes, and dichloromethane was added until a clear homogenous solution was observed; then, it was kept at −20 °C for a few days to get the desired material as an off-white solid (1.12 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, J = 3.2 Hz, 1H), 7.76−7.83 (m, 3H), 7.26−7.29 (m, 2H), 5.97 (s, 1H), 5.83 (s, 1H), 2.51 (s, 3H), 2.46 (s, 3H), 2.25 (s, 3H), 2.16 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.5, 153.5, 150.5, 149.4, 149.1, 145.1, 141.7, 137.2, 123.9, 122.0, 111.3, 106.8, 82.7, 14.4, 14.0, 13.9, 11.2. HRMS (ESI-TOF) m/z: [M + Na]$^+$, calcd for $C_{17}H_{19}N_5O_2Na$, 348.1431; found, 348.1431, difference −0.07 ppm.

Resubmission of Carbamate (9) under DMAP Conditions. In a vial, carbamate intermediate **9** (163 mg, 0.500 mmol, 1.0 equiv) and quinuclidine (5.6 mg, 0.05 mmol, 0.1 equiv) were dissolved in THF, the vial headspace was purged briefly with nitrogen, and then, it was sealed and stirred at 60 °C using an aluminum block for 24 h. Then, all volatiles were removed in vacuo, and the residue was analyzed in DMSO-d_6 with 1,4-dioxane as an internal reference standard.

Mechanistic Crossover Experiment between Methanones 2a and 2b. To one vial were added *bis*(3,5-dimethylpyrazol-1-yl)methanone (**2a**) (109 mg, 0.500 mmol, 1 equiv), *bis*(pyrazol-1-yl)methnaone (**2b**) (81 mg, 0.50 mmol, 1 equiv), DMAP (12.2 mg, 0.100 mmol, 0.2 equiv), and THF (3 mL). A second vial was charged with the same reagents and amounts except with no DMAP added. Both solutions were stirred at 60 °C using an aluminum block for 5 h and then cooled to room temperature. All volatiles were evaporated; then, the residues were redissolved in $CDCl_3$ with 1,4-dioxane as an internal reference standard.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02442.

Spectral characterization for all compounds, Hammett analysis data plots, and crude NMRs for resubmission experiments (PDF)

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

TBD, 1,5,7-triazabicyclodec-5-ene; DBU, 1,8-diazabicycloundec-7-ene; THF, tetrahydrofuran; DMAP, 4-(*N*,*N*-dimethylamino)pyridine

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