

# Dehydrogenative Syntheses of Biazoles via a “Pre-Join” Approach

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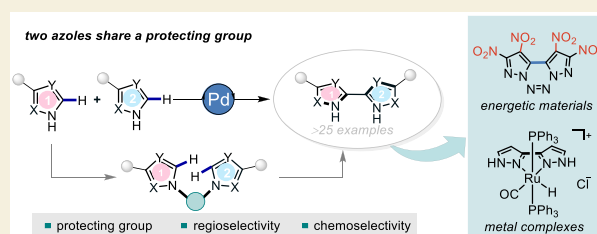
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**ABSTRACT:** The structural motif of biazoles is the predominant substructure of many natural products, pharmaceuticals, and organic materials. Considerable efforts have focused on synthesizing these compounds; however, a limited number of processes have been reported for the efficient formation of biazoles. Herein, we report a “pre-join” approach for the dehydrogenative synthesis of biazoles, which are challenging to prepare using conventional methods. A bench-stable and easily synthesized pyrazine-based group is critical for this transformation. This strategy enables the homocoupling of biazoles and the heterocoupling of two different azoles. Due to the broad substrate scope, this strategy exhibits potential for use in other fields, such as medicine, materials, and natural product chemistry.

**KEYWORDS:** biazoles, dehydrogenative coupling, bipyrazoles, energetic material, C–H activation



Biazoles are critical structural motifs often observed in natural products, functional materials, and molecules of medicinal interest (Figure 1).<sup>1–5</sup> For example, the weakly basic nitrogen atoms of deprotonated bipyrazoles have been applied in coordination chemistry, particularly to access coordination polymers and metal–organic frameworks.<sup>6–8</sup> Due to its conjugated system and nitrogen-rich backbone, bipyrazole is also an excellent platform for designing high-energy propellants and explosives.<sup>9</sup>

Despite the high application potential of nitrogen-rich bipyrazole compounds in materials chemistry and as tunable ligands in coordination chemistry, the lack of a general method for their synthesis is a significant bottleneck for their application.<sup>10</sup> A traditional method of preparing bipyrazoles involves the condensation reaction of 1,3-dicarbonyl com-

pounds with hydrazine (Scheme 1A).<sup>11</sup> However, not only are double condensation reactions challenging to control but also there is a lack of dicarbonyl compounds. This has hampered the facile preparation of bipyrazole-based compounds.

In recent years, the catalytic dehydrogenative dimerization of heteroarene has attracted considerable attention, as it is straightforward and step-economical.<sup>12–33</sup> However, a general strategy for such transformations to form biazoles still needs to be developed, and some formidable challenges still need to be overcome in this area (Scheme 1B).<sup>34–39</sup> First, the regioselectivity of the coupling reaction is problematic. For example, pyrazole contains three different C–H bonds, and the coupling of pyrazoles can yield six isomers. Second, controlling the chemoselectivity of dehydrogenative coupling between two different azoles remains challenging because of the competition between heterocoupling and homocoupling.<sup>40,41</sup> To address these challenges, we envisaged a “pre-join” approach for the facile synthesis of various free biazoles. As shown in Scheme 1C, introducing a “pre-join” group at the NH position of the two bipyrazoles should enable intramolecular dehydrogenative coupling to yield a fused ring. The subsequent removal of this group ultimately yields a bipyrazole derivative. The merits of this strategy are 3-fold. (1) The regio- and chemoselectivities are improved because of the nature of the intramolecular

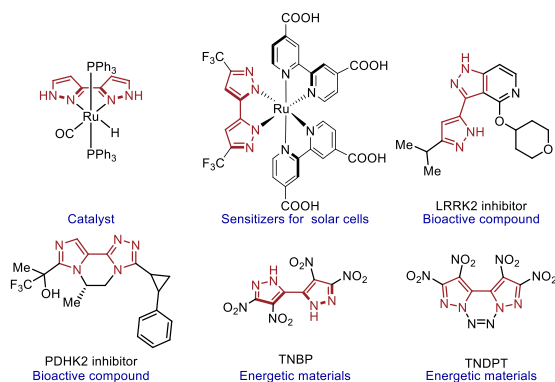


Figure 1. Examples of important bipyrazole compounds.

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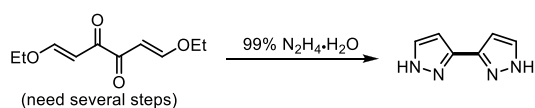
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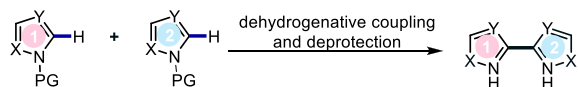


## Scheme 1. Synthesis of Biazoles

## A traditional method



## B dehydrogenative coupling



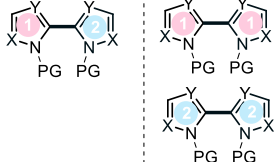
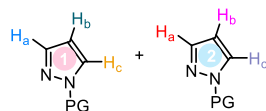
■ step-economical ■ atom-economical

regioselectivity  
up to 6 isomers

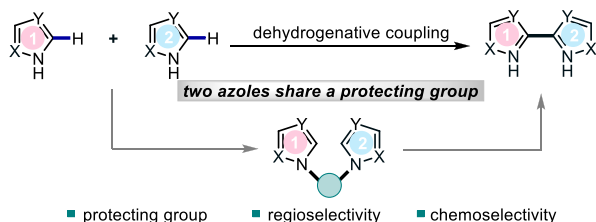
Challenges

chemoselectivity

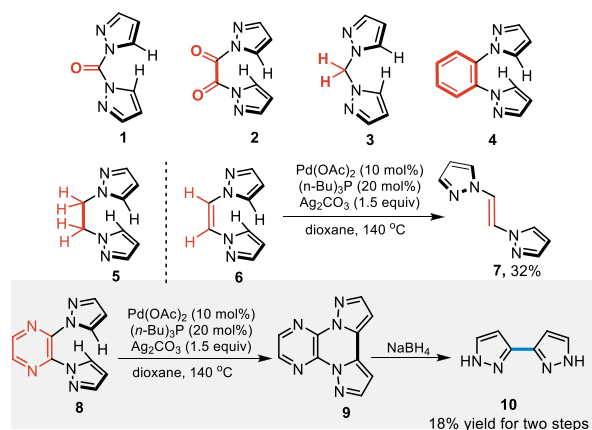
crosscoupling VS homocoupling



## C. this work: "Pre-join" approach

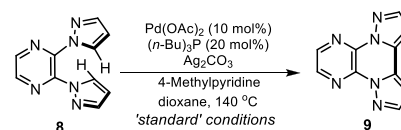


## Scheme 2. Synthesis of Bipyrazoles



reaction.<sup>42–44</sup> (2) This "pre-join" group also acts as a protective group; hence, it is unnecessary to use other protective groups. (3) Asymmetrical biazole derivatives may be readily synthesized by linking two different azoles to the "pre-join" group.

The choice of a "pre-join" group is crucial to the success of the transformation. Thereafter, the coupling of pyrazoles was employed as a model reaction to investigate the proposed "pre-join" strategy (Scheme 2). We conducted a coupling study in the presence of Pd(OAc)<sub>2</sub>, (*n*-Bu)<sub>3</sub>P, and Ag<sub>2</sub>CO<sub>3</sub> as oxidants. When carbonyl (1), 1,2-dicarbonyl (2), and methylene (3) groups were used, the desired cross-coupling products were not obtained and the starting materials decomposed under the

Table 1. Screening of Reaction Conditions<sup>a,b</sup>

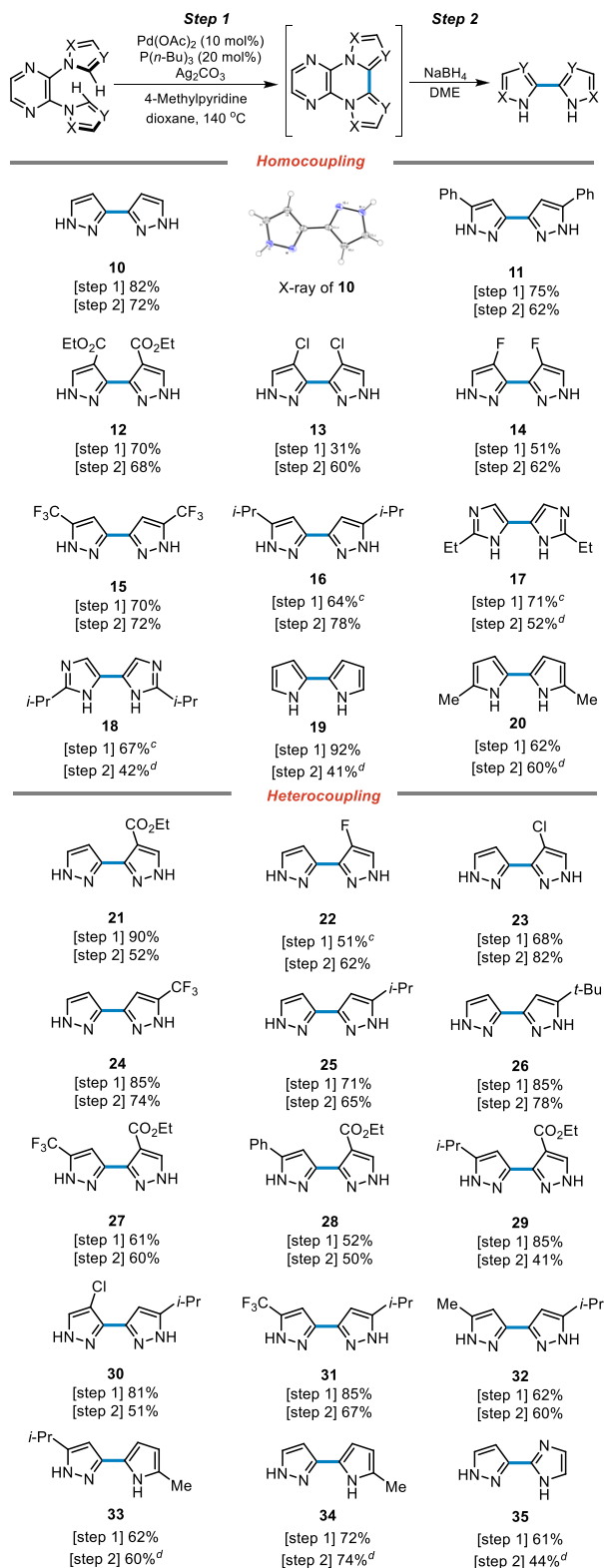
entry	variation from "standard" conditions	yield (%)
1	none	82
2	PPh <sub>3</sub> instead of ( <i>n</i> -Bu) <sub>3</sub> P	<10
3	P( <i>t</i> -Bu) <sub>3</sub> instead of ( <i>n</i> -Bu) <sub>3</sub> P	<10
4	PMe <sub>3</sub> instead of ( <i>n</i> -Bu) <sub>3</sub> P	<10
5	without 4-methylpyridine	36
6	4-(trifluoromethyl)pyridine instead of 4-methylpyridine	58
7	4-methoxypyridine instead of 4-methylpyridine	45
8	DABCO instead of 4-methylpyridine	33
9	in toluene	41
10	in xylene	38
11	without Pd(OAc) <sub>2</sub>	0
12	Pd(OAc) <sub>2</sub> (5 mol %) and ( <i>n</i> -Bu) <sub>3</sub> P (10 mol %)	52

<sup>a</sup>Reaction conditions for step 1: **8** (0.2 mmol), Pd(OAc)<sub>2</sub> (0.02 mmol), P(*n*-Bu)<sub>3</sub> (0.04 mmol), Ag<sub>2</sub>CO<sub>3</sub> (0.3 mmol), 4-methylpyridine (0.42 mmol), and 1,4-dioxane, at 140 °C for 24 h. <sup>b</sup>Isolated yields after chromatography.

coupling conditions. When compounds **4** and **5** were used, the desired coupling products were obtained in good yields. However, the removal of the "pre-join" groups after coupling was challenging. When compound **6** was used, the configuration of the olefins was reversed, and compound **7** was obtained under the coupling conditions. However, pyrazine was adequate; the reaction using 2,3-dichloropyrazine proceeded under mild conditions, and the coupling yielded the desired product **9**.<sup>45</sup> Moreover, the pyrazine moiety could be readily removed after coupling, furnishing the free bipyrazole product **10**.

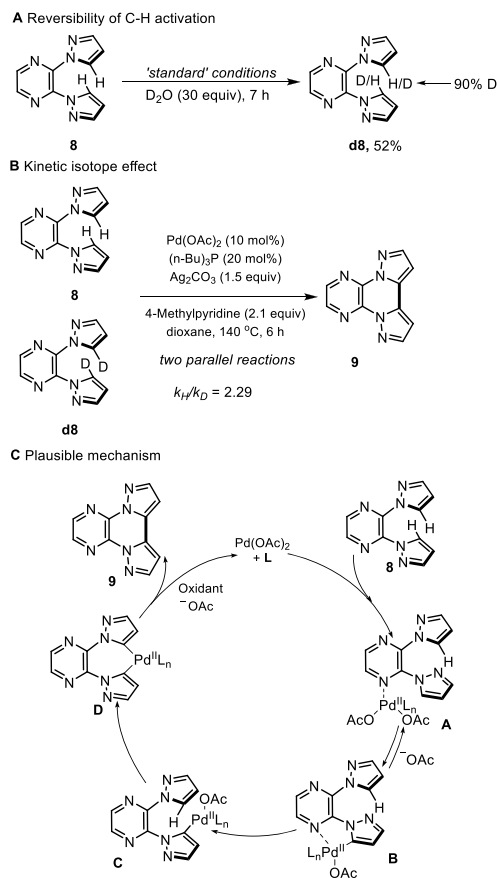
Subsequently, we tested different reaction conditions for the Pd-catalyzed intramolecular coupling using dipyrazole pyrazine **8** as a model substrate. After careful optimization of all reaction parameters, fused product **9** was obtained in 82% yield using a combination of Pd(OAc)<sub>2</sub>/*n*-Bu<sub>3</sub>P, Ag<sub>2</sub>CO<sub>3</sub> as an oxidant, and 4-methylpyridine as an additive in dioxane (Table 1, entry 1). The reaction efficiency strongly depended on the nature of the ligand. Less electron-rich PPh<sub>3</sub> and sterically hindered P(*t*-Bu)<sub>3</sub> were found to be much less effective (Table 1, entries 2 and 3). However, less sterically hindered PMe<sub>3</sub> also resulted in much lower efficiency (Table 1, entry 4), thus suggesting the need for an electron-rich and appropriate sterically hindered phosphine (see the Supporting Information for detailed ligand screening). Various additives were evaluated to further improve the yield (Table 1, entries 5–8), wherein adding 4-methylpyridine enhanced the yield. Pyridine is often used as an additive in Pd-catalyzed oxidation reactions, which is likely to stabilize the Pd(II) catalyst.<sup>46–49</sup> In addition, dioxane as the solvent proved superior to toluene and xylene (Table 1, entries 9 and 10). Furthermore, no coupling occurred without the Pd catalyst (Table 1, entry 11), whereas the product was obtained in 52% yield with a 5 mol % catalyst loading (Table 1, entry 12).

We then investigated the substrate scope of dehydrogenative coupling (Scheme 3). Although the one-pot procedure provided the desired biazole products in useful yields, the two-step procedure generally resulted in a higher overall

Scheme 3. Substrate Scope<sup>a,b</sup>

<sup>a</sup>Reaction conditions: step 1, substrate (0.2 mmol), Pd(OAc)<sub>2</sub> (0.02 mmol), P(*n*-Bu)<sub>3</sub> (0.04 mmol), Ag<sub>2</sub>CO<sub>3</sub> (0.3 mmol), 4-methylpyridine (0.42 mmol), and 1,4-dioxane, at 140 °C for 24 h; step 2, NaBH<sub>4</sub> (4 equiv), 1,2-dimethoxyethane, 105 °C. <sup>b</sup>Yields upon isolation. <sup>c</sup>Without 4-methylpyridine. <sup>d</sup>Step 2: LiAlH<sub>4</sub> (4 equiv), 1,4-dioxane, 100 °C.

## Scheme 4. Mechanistic Investigations



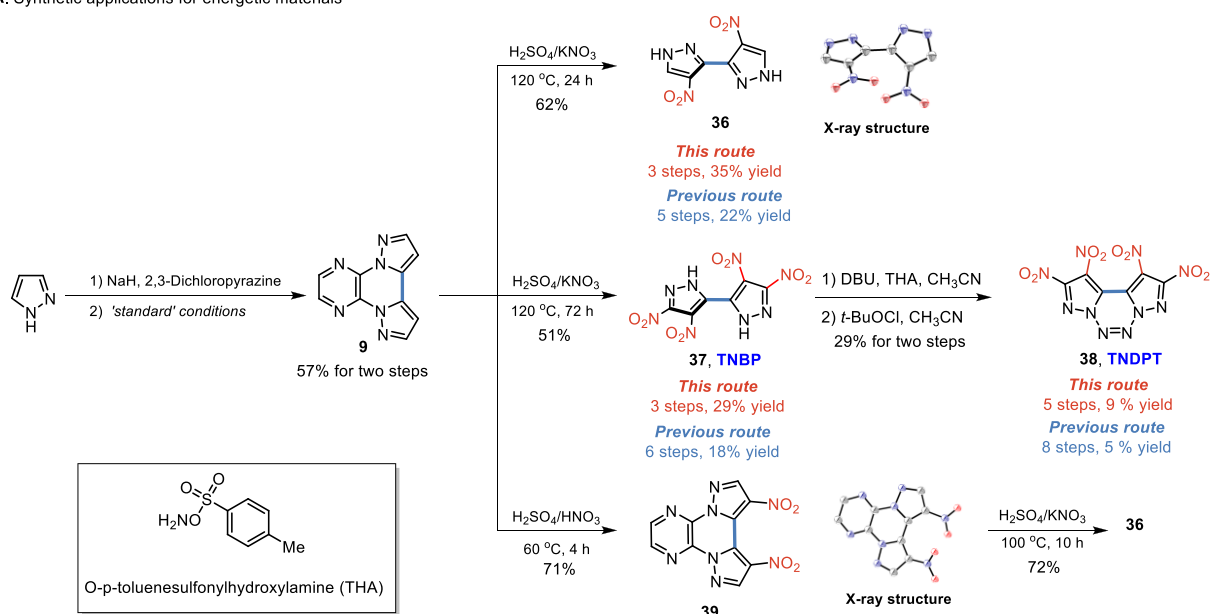
efficiency. Moreover, this system was highly tolerant to various functional groups on pyrazole rings, such as phenyl (**11**), ester (**12**), chloride (**13**), fluoride (**14**), and trifluoromethyl (**15**). Oligomers of the starting materials were not observed. Sterically hindered pyrazoles also underwent dimerization, and the corresponding product (**16**) was generated at a moderate yield. Unfortunately, substrates bearing carboxylic acid or nitro groups could not be constructed from the corresponding pyrazole. Several sensitive functional groups, such as amide and nitrile, were incompatible with the reaction conditions (see the [Supporting Information](#) for details). Furthermore, other heteroaromatic compounds, such as imidazole and pyrrole, were also suitable for developing symmetrical products (**17–20**) in moderate yields. Using our protocol, biimidazole ligand **17** was synthesized in three steps. The literature method to synthesize **17** involved a linear five-step reaction using the same starting material, 2-ethylimidazole.<sup>50</sup>

We then investigated the method for the challenging heterocoupling of two different azoles. Various asymmetrical bipyrazole products were obtained in good to moderate yields. Electron-deficient substituents such as ester (**21, 27–29**), fluoride (**22**), chloride (**23**), and trifluoromethyl (**24, 27**, and **31**) groups were well tolerated. Substrates bearing electron-donating substituents, such as *tert*-butyl (**26**), methyl (**32**), and isopropyl (**25, 30–32**) groups, have also been successfully coupled, highlighting the versatility of the transformation.

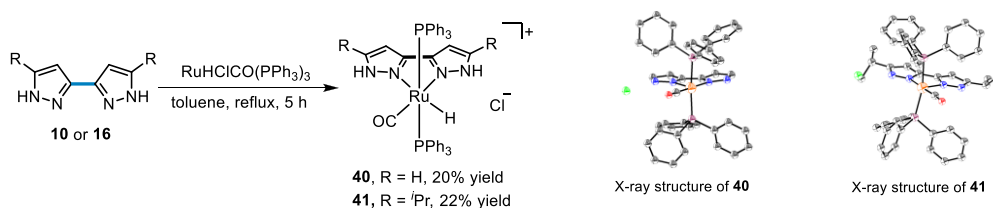
The scope of this reaction was also investigated for two different heteroaromatic compounds. The reactions between pyrazole and pyrrole (**33** and **34**) and pyrazole and imidazole

## Scheme 5. Synthetic Applications

## A. Synthetic applications for energetic materials



## B. Synthetic applications for metal complexes



(35) proceeded smoothly to generate the corresponding products in moderate yields. Notably, no homocoupling products were detected by crude <sup>1</sup>H NMR analysis.

We performed a series of mechanistic studies to investigate this reaction mechanism. The reaction in the presence of D<sub>2</sub>O yielded deuterated products, indicating a rapid and reversible C–H metalation step (Scheme 4A). Intermolecular kinetic isotope effects were investigated (Scheme 4B). Compounds **8** and **d8** were dimerized in parallel, with a significant isotopic effect ( $k_H/k_D = 2.29$ ). Therefore, C–H bond cleavage played an essential role in this reaction. Hg poisoning experiments were carried out. Addition of Hg to an ongoing reaction mixture led to immediate inhibition, which suggests that the active catalyst consists of palladium nanoparticles during the reaction. Based on previous studies and our observations, a plausible mechanism is proposed (Scheme 4C). The reaction was initiated by the coordination of dipyrazole pyrazine **8** to the Pd(II) species, followed by a reversible C–H activation step that generates the Pd(II) complex **B**. Further, the rotation of pyrazole generates complex **C**, which prompts C–H palladation of the second pyrazine moiety, yielding complex **D**. Subsequent reductive elimination leads to the formation of the coupling product **9** along with a Pd(0) species. The catalytic cycle is closed through the reoxidation of Pd(0) to Pd(II) by silver salt.

This approach provides a convenient route to accelerate the synthesis of energetic compounds (Scheme 5A), such as the synthesis of 4,4'-dinitro-1*H*,1'-*H*-3,3'-bipyrazole (**36**), which is not only an insensitive heat-resistant explosive with good

properties but also a critical intermediate in synthesizing high-performance energetic materials and energetic oxidizers for diverse propellants.<sup>51</sup> Nitration of **9** with a mixture of KNO<sub>3</sub>/H<sub>2</sub>SO<sub>4</sub> generated **36** at 62% yield. In comparison, the synthesis of **36** required five steps at a 22% overall yield.<sup>52</sup> The second example involved synthesizing 4,4',5,5'-tetranitro-2*H*,2'*H*-3,3'-bipyrazole (TNBP) (**37**), which displays energetic properties comparable to those of RDX and a far superior thermal stability and lower sensitivity. TNBP was easily synthesized via the direct nitration of **9** with a mixture of KNO<sub>3</sub> and H<sub>2</sub>SO<sub>4</sub> at 120 °C for 72 h. The previous synthesis of TNBP required six steps with an 18% overall yield.<sup>53</sup> More significantly, TNBP is a key precursor of 1,2,9,10-tetranitrodipyrazolo[1,5-*d*:5',1'-*f*][1,2,3,4]tetrazine (TNDPT) (**38**), which exhibits excellent detonation performance comparable to that of CL-20, rendering it attractive for use in high-performance energetic materials. Similarly, using our protocol, TNDPT was prepared in five steps, with an overall yield of 9%. The literature method to synthesize TNDPT involved eight steps, with a 5% overall yield.<sup>54</sup> Finally, nitration of **9** with an acid mixture (H<sub>2</sub>SO<sub>4</sub> + 100% HNO<sub>3</sub>) at 60 °C generated compound **39** with a dinitro-fused ring in a 71% yield. Further nitration of **39** over extended reaction times and high temperatures generated **36** in a 72% yield.<sup>55</sup> Bipyrazoles are privileged skeletons that act as bidentate ligands in metal-catalyzed reactions.<sup>56</sup> However, traditional methods for preparing such ligands are often inefficient and involve multistep synthesis. This study provides a simple and distinct approach for accessing various biazole ligands (Scheme 5B).

Biazole compounds **10** and **16** were treated with RuHClCO<sub>3</sub>(PPh<sub>3</sub>)<sub>3</sub>, affording the corresponding Ru complexes **40** and **41**. Their structures were confirmed by X-ray crystallography.

In summary, we developed a “pre-joined” strategy for the facile synthesis of biazole derivatives. This coupling mode enables rapid biazole syntheses with simple reagents and is favorable for practical synthetic applications. Remarkably, the preparation of the energetic materials TNBP and TNDPT and bipyrazole ligands was shown to be viable using the designed protocol. Hence, we demonstrated a valuable strategy for synthesizing biazole molecules, which has potential applications in medical, material, and natural-product chemistry.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacsau.2c00597>.

Experimental procedures, characterization data, and spectra for all new compounds (PDF)

Crystallographic data for **10** (PDF)

Crystallographic data for **36** (PDF)

Crystallographic data for **39** (PDF)

Crystallographic data for **40** (PDF)

Crystallographic data for **41** (PDF)

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## Author Contributions

T.Y., Y.W., and Y.D. contributed equally. CRediT: **Tianyang Yu** investigation, methodology; **Yan Wang** methodology, validation; **Yaqun Dong** investigation.

## Notes

The authors declare no competing financial interest.

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