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Rhodium-Catalyzed Denitrogenative Diazole–Triazole Coupling toward Aza-Bridged Structures and Imidazole-Based Chelating Ligands

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Cite This: *Org. Lett.* 2021, 23, 4173–4178 Read Online

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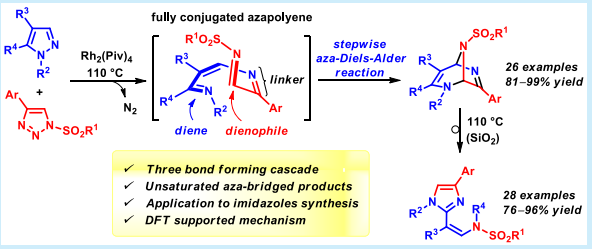
ABSTRACT: 1,4,8-Triazaocta-1,3,5,7-tetraenes, generated in situ by $Rh_2(Piv)_4$-catalyzed denitrogenative coupling of pyrazoles with 1-sulfonyl-1,2,3-triazoles, smoothly form 2,6,8-triazabicyclo[3.2.1]octa-3,6-dienes via intramolecular aza-Diels–Alder cycloaddition. This domino reaction, combined with the subsequent thermal or acid-catalyzed rearrangement of the cycloadducts, provides direct and flexible access to *N*-sulfonylated (*Z*)-2-(2-aminovinyl)imidazoles.

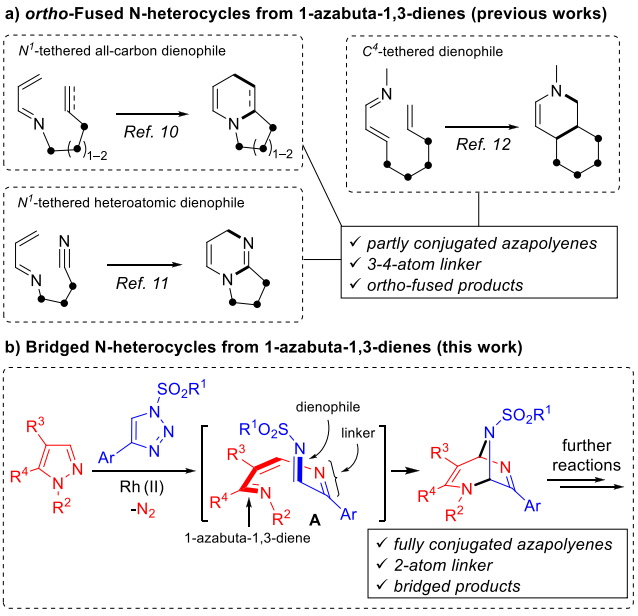


Azabuta-1,3-dienes are valuable intermediates in the synthesis of various heterocycles, functionalized carbocycles, and nitrogen-containing chiral scaffolds.[1] The unique feature of azapolyene building blocks is in their extremely wide reactivity, including various pericyclic and pseudopericyclic transformations as well as ionic addition reactions. These reactions underlie a great deal of highly atom-economical and regio- and stereoselective syntheses of four-,[2] five-,[3] six-,[4] seven-,[5] eight-,[6] nine-,[7] and ten-membered[8] nitrogen heterocycles. This methodology can also be applied to polycyclic systems, but their scope is restricted exclusively to *ortho*-fused heterocycles. The intramolecular aza-Diels–Alder (IMADA) reaction of 1-azabuta-1,3-dienes bearing tethered dienophile units is one effective approach to these compounds.[9] It allows the formation of two rings in a highly stereoselective fashion in one synthetic operation. In particular, this approach was used for the preparation of several pyrido- and pyrimido-fused systems by intramolecular trapping of 1-azabuta-1,3-dienes with a carbon–carbon π bond or cyano group, respectively (Scheme 1a).[10−12] The dienophile can be attached to the N1 or C4 atom of the 1-azabutadiene by a three- or four-atom linker, at least one atom of which is sp^3-hybridized.

To the best of our knowledge, there are no examples in the literature of the intramolecular trapping of azabutadienes with a dienophile tethered with a two-atom linker. In addition, there are still no answers to the following questions: (a) whether the IMADA reaction can lead to the formation of bridged products and (b) whether a fully conjugated azapolyene is capable of undergoing the IMADA reaction.

We recently found that rhodium α-carbonyl carbenes derived from α-diazo esters were able to cleave the pyrazole ring to form unstable 1,5-diazahexa-1,3,5-trienes, which smoothly cyclized to give 1,2-dihydropyrimidine derivatives.[13]

Scheme 1. IMADA Reactions of 1-Azabuta-1,3-dienes



Received: April 1, 2021
Published: May 17, 2021

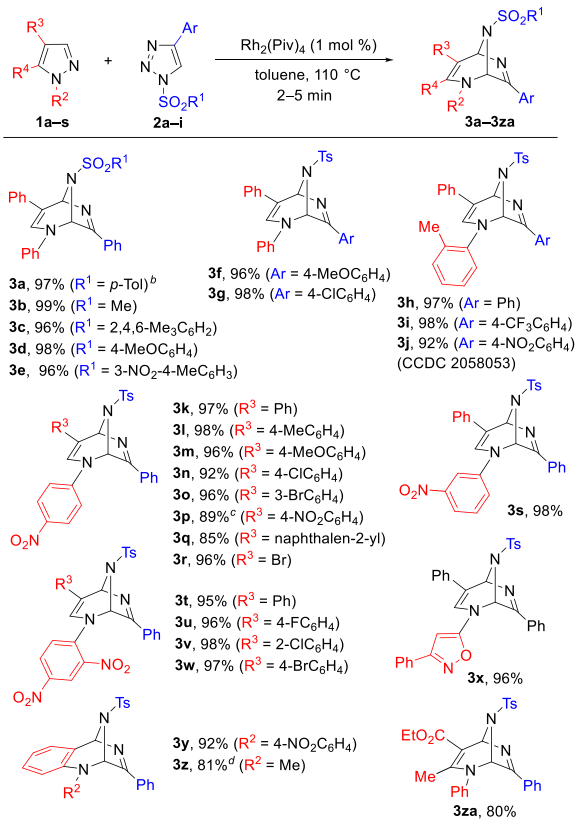
https://doi.org/10.1021/acs.orglett.1c01092
Org. Lett. 2021, 23, 4173–4178

This result motivated us to examine the reactivity of rhodium azavinylcarbenes[14] toward pyrazoles in the hope of finding a route to hitherto unknown 1,4,8-triazaocta-1,3,5,7-tetraenes **A** (Scheme 1b). It was expected that the additional C═N bond in these compounds could dramatically change the mode of heterocyclization and, in particular, makes possible the formation of bridged structures with a high degree of unsaturation.

Herein we describe an unprecedented Rh(II)-catalyzed denitrogenative coupling reaction of 1,2,3-triazoles with pyrazoles that proceeds via IMADA stepwise cycloaddition of the two-atom-linked azadiene−azadienophile intermediates—1,4,8-triazaocta-1,3,5,7-tetraenes **A** (Scheme 1b). The reaction was applied for the preparation of bridged compounds of the 2,6,8-triazabicyclo[3.2.1]octa-3,6-diene series, which turned out to be excellent precursors of new (aminovinyl)imidazoles. The mechanistic insight into the reaction has been revealed by DFT calculations.

We initiated our studies with the test reaction of pyrazole **1a** with 1,2,3-triazole **2a**, used as a source of the rhodium azavinylcarbene, in the presence of $Rh_2(Piv)_4$ (1 mol %) in toluene at 110 °C. To our delight, the reaction proceeded smoothly to afford 2,6,8-triazabicyclo[3.2.1]octa-3,6-diene **3a** in 97% yield (Scheme 2). $Rh_2(OAc)_4$ also catalyzed the reaction, but the yield of **3a** did not exceed 90% even at a catalyst loading of 5 mol %. Bicycle **3a** is a formal adduct of the intramolecular aza-Diels−Alder reaction between the 1-azabuta-1,3-diene and electron-deficient aldimine azadienophile.

Scheme 2. Scope of Triazabicyclooctadienes 3[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Rh_2(Piv)_4$ (1 mol %), toluene (1 mL), 110 °C, 2−5 min, in a sealed tube. [b]The yield of **3a** was 90% according to ^{1}H NMR spectroscopy when 5 mol % $Rh_2(OAc)_4$ was used. [c]PhCl (2 mL), 131 °C. [d]$Rh_2(Piv)_4$ (5 mol %), 0.5 h.

Since it was the first example of the IMADA reaction of a fully conjugated azapolyene, we further studied the scope of the reaction using a wide range of pyrazoles **1** and 1,2,3-triazoles **2** (Scheme 2). Varying the Ar and R^1-sulfonyl substituents in the 1,2,3-triazole ring had no noticeable effect on the yield of products **3b−j** which was nearly quantitative in all cases. Pyrazoles **1c−p** bearing both electron-donating and electron-withdrawing aryl substituents at the N1 and C4 positions smoothly reacted with **2a** to afford triazabicyclooctadienes **3k−x** in high yields.

Remarkably, pyrazole **1p** containing an isoxazolyl substituent, which can react with rhodium azavinylcarbenes,[15] underwent the transformation of the pyrazole ring exclusively to afford triazabicyclooctadiene **3x** in 92% yield. Benzo-fused pyrazole substrates, *N*-aryl- and *N*-methyl-1*H*-indazoles **1q** and **1r**, also proved to be suitable in this protocol and gave bridged fused-ring compounds **3y** and **3z** in high yields. The reaction of 4,5-disubstituted pyrazole **1s** with **2a** gave adduct **3za** in good yield as well. These examples provide a good illustration of the low sensitivity of the product yield to the nature of the C4 and C5 substituents in the pyrazole.

Further exploration of the scope of the reaction using *N*-alkylpyrazoles revealed rather unexpected reactivity of triazabicyclooctadienes **3**. The reaction of **2a** with **1t** (1 mol % $Rh_2(Piv)_4$, toluene, 110 °C, 30 min) gave an inseparable mixture of the corresponding adduct **3** and (*Z*)-2-(2-aminovinyl)imidazole **4a** in comparable amounts (Scheme 3). However, further heating for 3 h resulted in the formation of imidazole **4a** (57%) as the only product. 2-(2-Aminovinyl)-imidazoles are scarcely known, likely because of the lack of reliable and convenient methods for their synthesis.[16] This fact prompted us to study this reaction in more detail. It was found that an increase in the catalyst loading to 5 mol % led to an increase in the yield of imidazole **4a** up to 87%.

The scope of the imidazole synthesis was then investigated using a wide range of *N*-alkylpyrazoles (Scheme 3). The reaction smoothly proceeded with pyrazoles bearing various aryls, 3-indolyl, and benzoyl at C4 (imidazoles **4a−i**). It is gratifying that the reaction is almost insensitive to the nature of the *N1*-alkyl substituent in the pyrazole (imidazoles **4j−n**, **4q**). The synthetic applicability of this method was demonstrated by the gram-scale synthesis of imidazole **4l** (93%, 1.41 g).

Next, we returned to *N*-arylpyrazoles as attractive starting materials for the preparation of 1-aryl-substituted imidazoles **4**. Initially, *N*-phenylpyrazole **1a**, triazole **2a**, and 5 mol % $Rh_2(Piv)_4$ were heated for 5 min to form bicycle **3a** (see Scheme 2). When this reaction mixture was further heated at 110 °C for 16 h, **3a** isomerized to imidazole **4o** in 89% yield (Scheme 3). Under the same conditions, *N*-*o*-tolylpyrazole **1b** gave imidazole **4p** within 14 h in 90% yield. The addition of silica gel to the reaction mixture significantly increased the reaction rate and slightly increased the yield of **4p** to 96%. Imidazole **4p** can also be obtained directly from bicycle **3h** by heating in toluene at 120 °C for 2 h in the presence of silica gel (see Table S1 in the Supporting Information).

N-Sulfonyltriazoles are known to react with nitriles under rhodium catalysis to yield *N*-sulfonylimidazoles.[14e] Expectedly, the $Rh_2(Piv)_4$-catalyzed reaction of *N*-(2-cyanobenzyl)-substituted pyrazole **1zi** with a 3-fold excess of triazole **2a** afforded diimidazole derivative **4x** in high yield.

https://doi.org/10.1021/acs.orglett.1c01092
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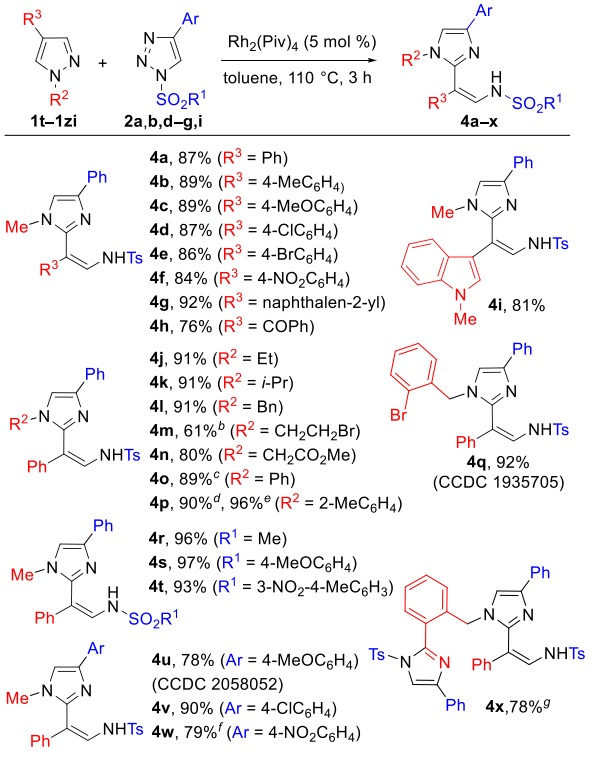
Scheme 3. Scope of Imidazoles 4[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Rh_2(Piv)_4$ (5 mol %), toluene (1 mL), 110 °C, 3 h, in a sealed tube. [b]1.5 h. [c]16 h. [d]14 h. [e]Silica gel, 120 °C, 1.5 h. [f]PhCl (2 mL), 131 °C. [g]**2a** (0.6 mmol).

The proposed mechanism for the formation of compounds **3zb** and **4r** from pyrazole **1t** and triazole **2b** under $Rh_2(OAc)_4$ catalysis is presented in Figure 1. It involves an initial attack of rhodium azavinylcarbene **5**, derived from triazole **2**, onto N2 of pyrazole **1** to give pyrazolium ylide complex **6**. The possible routes for the transformation of complex **6** to **3zb** and then to **4r** were simulated by the DFT method (B3LYP/6-31+G(d,p)/Stuttgart RSC 1997 ECP) (see section 9 in the Supporting Information). The calculations revealed that the formation of 1,4,8-triazaocta-1,3,5,7-tetraene **8** from complex **6** does not occur directly but rather involves two steps: the formation of metal-free pyrazolium ylide **7** (TS1) followed by ring opening (TS2). The IMADA cycloaddition of triazatetraene **8** to bridged adduct **3zb** proceeds in a stepwise fashion featuring extremely low barriers for both steps (TS4 and TS5). According to the experimental data, the formation of imidazoles **4** from adducts **3** is catalyzed by acids. The role of the acid catalyst (proton was used in the calculations) is to accelerate the exchange by *N*-Me and *N*-Ms moieties in the largest and smallest bridges of the 2,6,8-triazabicyclo[3.2.1]-octa-3,6-diene framework (TS6−TS9) (see Figure S7 in the Supporting Information). The presence of a strong electron-withdrawing substituent (RSO_2) on the nitrogen atom of the three-atom bridge greatly weakens its bond with the bridge-head atom. As a result, the transformation of bicyclic isomer *syn*-**12** into zwitterion **13** has a very low barrier (TS10, $\Delta G^{\ddagger}$ = 9.0 kcal mol^{-1}). The rotation around the C−C single bond (TS11) followed by a low-barrier 1,4-prototropic shift (TS12) affords imidazole **4r**. The extremely low value of this barrier resulted from the formation of the aromatic imidazole ring.

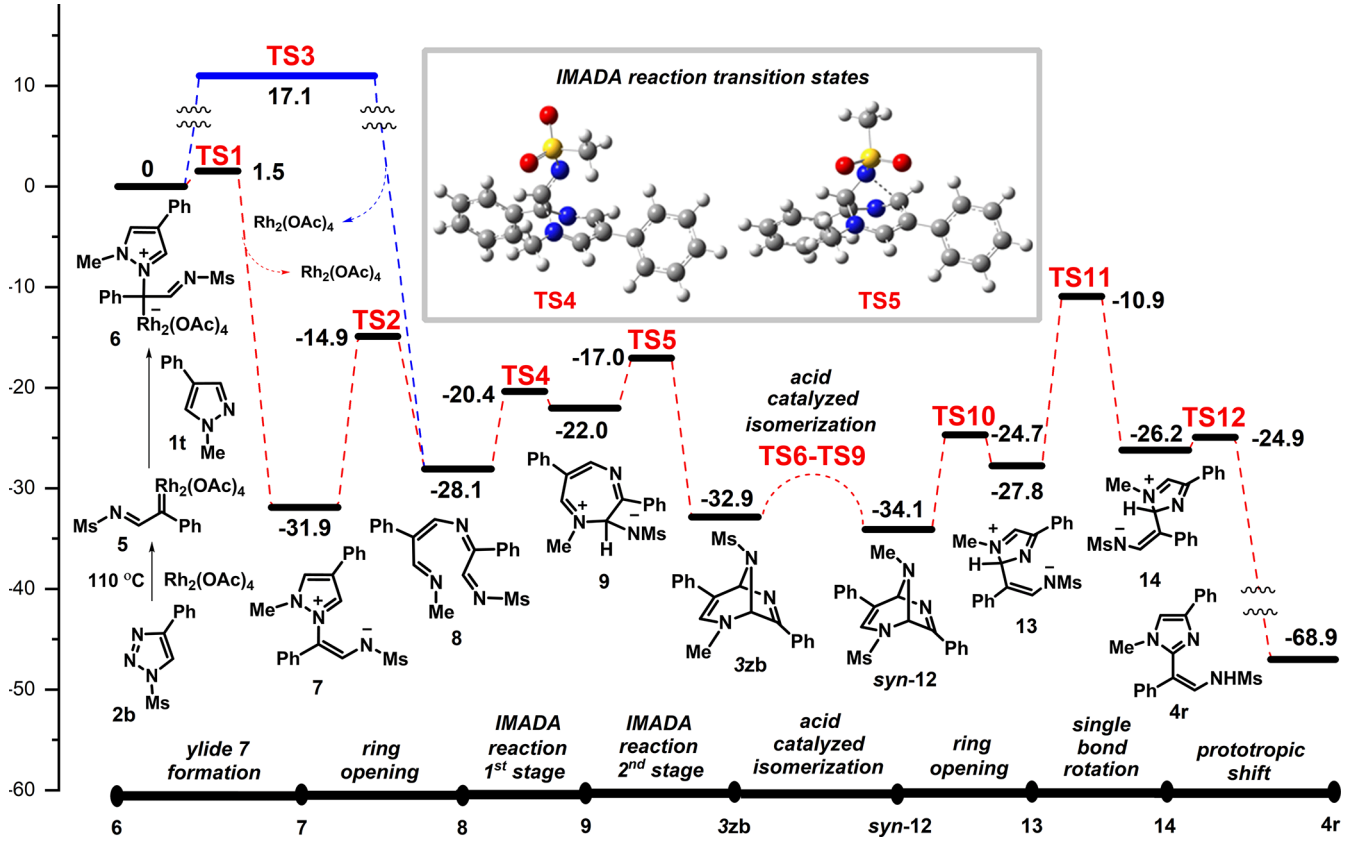


Figure 1. Energy profile (Gibbs free energies in kcal/mol) for the transformation of complex **6** into imidazole **4r**.

https://doi.org/10.1021/acs.orglett.1c01092
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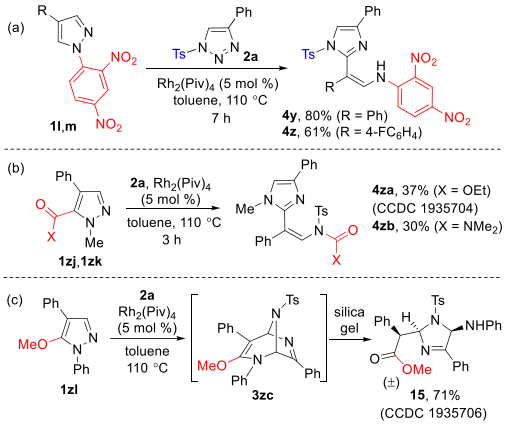
According to this mechanism, the pyrazoles with an electron-withdrawing substituent at N1 should produce primary bridged adducts like **3zb** that can be directly cleaved across the three-atom bridge, bypassing the catalytic isomerization **3** → **12**. Ultimately, this should result in the formation of 2-(2-aminovinyl)imidazoles with the sulfonyl substituent in the imidazole ring, not in the side chain. Indeed, the reaction of 2,4-dinitrophenyl-substituted pyrazoles **1l** and **1m** with triazole **2a** afforded 1-tosylimidazoles **4y** and **4z** in good yields (Scheme 4a). Thereby, the ring−ring tautomerism in bridged

Scheme 4. Synthesis of Compounds 4y, 4z, 4za, 4zb, and 15



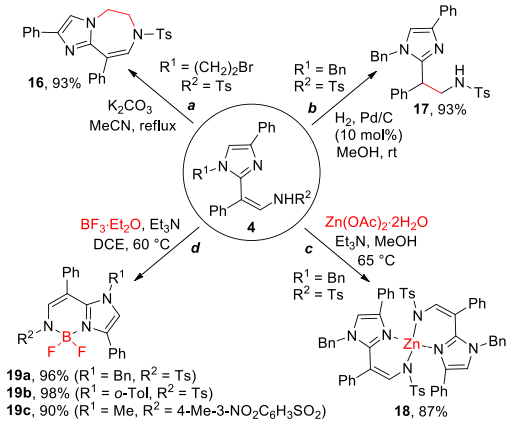
compounds **3** makes it possible to manage the location of the sulfonyl substituent in the final imidazoles **4** through the electronic effect of the N1 substituent in the pyrazole.

The synthesis of imidazoles **4za** and **4zb** from pyrazoles **1zj** and **1zk** bearing CO_2Et or $CONMe_2$ substituents at C5 demonstrated that the last stage of the domino reaction is not limited to prototropy but can also occur as the 1,4-shift of a carbonyl-containing group (Scheme 4b).

In contrast, the MeO substituent at C5 completely blocks the formation of imidazoles **4**. Thus, the reaction of 5-methoxypyrazole **1zl** with **2a** stopped at the formation of primary cycloadduct **3zc**, which was transformed into imidazoline **15** during chromatographic purification (Scheme 4c).

To demonstrate the utility of imidazoles **4** for the design of new heterocyclic systems and metal and boron complexes, some additional experiments were carried out (Scheme 5).

Scheme 5. Postsynthetic Transformations of Imidazoles 4



Imidazole **4m** was transformed into imidazo[1,2-*d*][1,4]-diazepine **16** in high yield via intramolecular nucleophilic substitution. The aminovinyl substituent of imidazole **4l** can be effectively reduced with hydrogen on Pd/C to afford imidazole **17**. Imidazole **4l** was used for the preparation of zinc complex **18** in 87% yield. Difluoroboron complexes **19a−c** were synthesized from imidazoles **4l**, **4p**, and **4t** in nearly quantitative yield.

In conclusion, we have demonstrated the high-yield synthesis of 2,6,8-triazabicyclo[3.2.1]octa-3,6-dienes by the $Rh_2(Piv)_4$-catalyzed domino reaction of pyrazoles with 1-sulfonyl-1,2,3-triazoles. The reaction proceeds via stepwise IMADA cycloaddition of the fully conjugated triazatetraene intermediates. (*Z*)-2-(2-Aminovinyl)imidazoles, the products of thermal or acid-catalyzed isomerization of the cycloadducts, were used for the preparation of boron and zinc complexes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01092.

Experimental procedures; characterization data; calculation details; X-ray data for compounds **3j**, **4q**, **4u**, **4za**, and **15**; and ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1935704−1935706, 2058052, and 2058053 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

https://doi.org/10.1021/acs.orglett.1c01092
Org. Lett. 2021, 23, 4173−4178

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of the Russian Science Foundation (17-13-01078). This research used resources of the Magnetic Resonance Research Centre, Chemical Analysis and Materials Research Centre, Computing Centre, Centre for X-ray Diffraction Studies, and Chemistry Educational Centre of the Research Park of St. Petersburg State University.

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