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Synthesis of Nitrogen Heterocycles via Photochemical Ring Opening of Pyridazine *N*-Oxides

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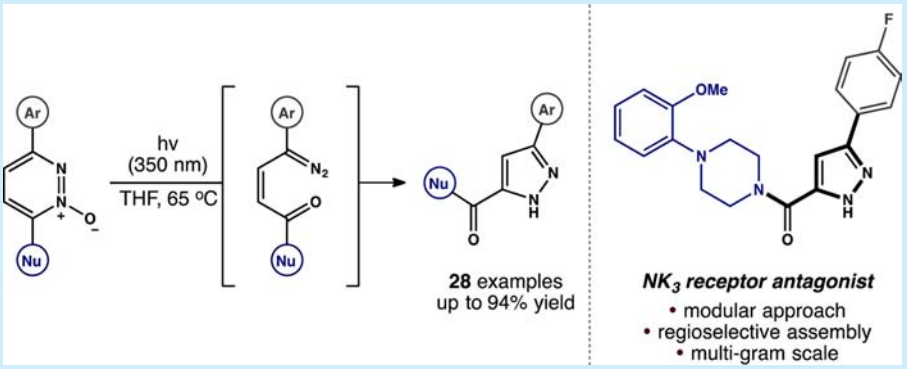
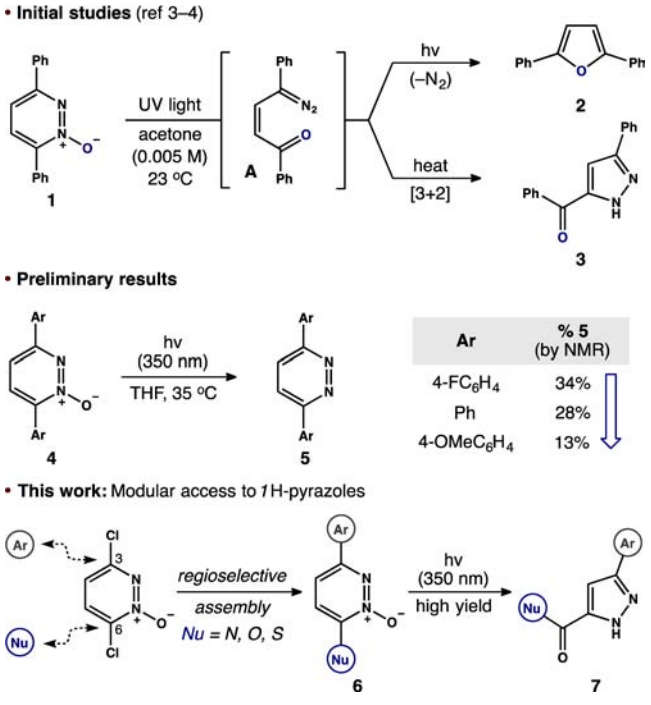
Supporting Information



ABSTRACT: A photochemical method for the direct synthesis of 1*H*-pyrazoles from pyridazine *N*-oxides was developed. This chemistry features a regioselective approach to nonsymmetrically substituted pyridazine *N*-oxides. Herein, we highlight the first strategic use of photoinduced ring-opening reactions of 1,2-diazine *N*-oxides for the preparative synthesis of nitrogen heterocycles.

Chemists noted as early as 1901 that oxidation of diazines increased their sensitivity to UV light.[1] This observation fueled interest in examining the photochemistry of heterocycle *N*-oxides decades later.[2] In 1968, Buchardt discovered that photolysis of 3,6-diphenylpyridazine *N*-oxide (**1**) afforded a mixture of the parent pyridazine, 2,5-diphenylfuran (**2**), and 3-benzoyl-5-phenylpyrazole (**3**, Scheme 1).[3] This intriguing reaction proceeds through (*Z*)-diazoenone **A**, which is transiently generated from **1** upon exposure to UV light. Thus, heterocycles **2** and **3** are formed via secondary reactions of intermediate **A**.[3b]

Scheme 1. Photochemistry of Pyridazine *N*-Oxides



Investigations by Buchardt focused on the photochemistry of **1**. In this system, rearrangement to **A** was the main photoreaction, enabling **3** to be isolated in 75% yield. Conversely, studies by Ogata and Igeta showed that photolysis of alkylpyridazine *N*-oxides resulted in photodeoxygenation.[4] This disparate reactivity, together with a marked absence of methods for the regioselective oxidation of nonsymmetrically substituted pyridazines, has hindered the utility of this chemistry. Indeed, to the best of our knowledge, the Buchardt rearrangement of **1** is the only example of a *productive* photoinitiated ring-opening reaction involving pyridazine *N*-oxides.[5,6]

The photochemistry of **1** captured our attention because both the ring-opening process and the secondary reactions of **A** appear well suited for applications in heterocycle synthesis. Further development of this chemistry, however, required a strategy to suppress deoxygenation. Encouraged by Sigwalt's report that electron-donating substituents slowed the photoreduction of

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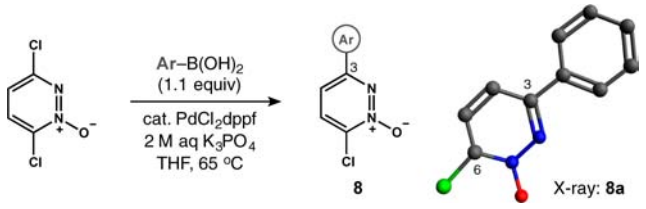
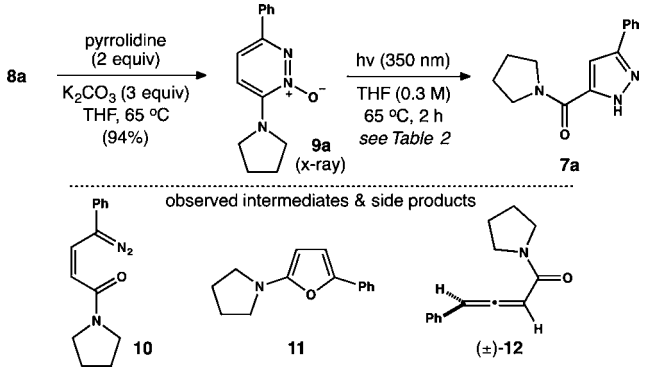
Table 1. Regioselective Suzuki Cross-Coupling of 3,6-Dichloropyridazine *N*-Oxide[a]



entry	[Pd] (mol %)	time (h)	Ar (product)	yield[b] (%)
1	3	2	Ph (**8a**)	93, 88[c]
2	3	1	Tol (**8b**)	99
3	3	0.5	1-naphthyl (**8c**)	97
4	3	2	4-OMeC$_6$H$_4$ (**8d**)	92
5	3	0.5	3,4-benzodioxyl (**8e**)	94
6	5	1	4-FC$_6$H$_4$ (**8f**)	88
7[d,e]	5	4	2,4-(Cl)$_2$C$_6$H$_3$ (**8g**)	70
8[d]	5	4	4-NMe$_2$C$_6$H$_4$ (**8h**)	72
9[d,f]	5	2	4-pyridinyl (**8i**)	73[g]

[a]Reaction conditions: 3,6-dichloropyridazine *N*-oxide (1.00 mmol), Ar-B(OH)$_2$ (1.1 equiv), aq K_3PO_4 (2 M, 1.5 mL·mmol^{-1} halide), $PdCl_2$dppf (3–5 mol %), THF (0.3 M), 65 °C. [b]Isolated yield after purification. [c]20.0 mmol scale. [d]Reaction run in dioxane (0.3 M) at 95 °C. [e]1.5 equiv Ar-B(OH)$_2$. [f]1.2 equiv Ar-B(OH)$_2$. [g]3,6-Dipyridinyl product isolated in 8% yield.

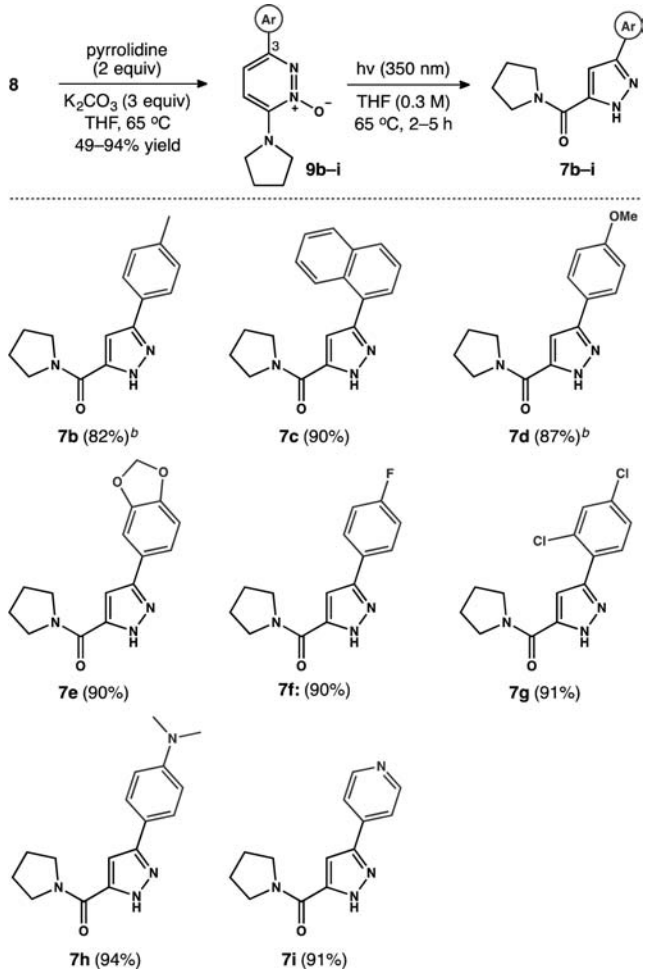
Table 2. Optimization and Control Experiments for the Photochemical Isomerization of 9a to 7a



entry	modification[a]	ratio[b] **7a**:**11**:**12**	**7a** yield[c] (%)
1	none	28:1:1	93
2	ambient light	no reaction	0
3	35 °C	7:2:1	65
4	THF (0.5 M)	20:2:1	69[d]
5	THF (0.1 M)	51:1:2	93
6	MeCN	ND	47[e]
7	MeCN (0.1 M)	47:0:1	92
8	MeOH	ND	60[e]
9	MeOH (0.1 M)	24:2:1	93
10	dioxane (0.1 M)	26:4:1	81
11	CH_2Cl_2	dec	ND
12[f]	$h\nu$ = 254 nm	11:2:1	40[d]
13[f]	$h\nu$ = 300 nm	8:2:1	67

[a]Reactions carried out at 65 °C unless otherwise indicated. [b]Determined by ^{1}H NMR of unpurified reaction mixtures. [c]Isolated yield after purification. [d]Unreacted **9a** observed. [e]Multiple side products observed along with **7a**, **11**, and **12**. [f]Photolysis carried out in dioxane (0.1 M). ND = not determined.

Scheme 2. Photochemical Isomerization of 3-Aryl-6-pyrrolidinylpyridazine *N*-Oxides[a]



[a]Isolated yields are reported and are an average of two experiments. [b]Furan side product was isolated in 5–9% yield.

pyridine *N*-oxides, we anticipated that perturbing the electronics of **1** would enable us to retain the *N*-oxide group.[7] A set of preliminary reactions supported this hypothesis (**4** → **5**, Scheme 1). Thus, we targeted structure **6** with the expectation that adding a heteroatom substituent to the pyridazine nucleus would enhance the desired photochemistry. If successful, this design would allow us to harness the photoinduced ring opening of **6** in a general way while concurrently establishing a new route to 1*H*-pyrazoles of significant utility (e.g., **7**).[8,9] Our development of this method, which features a regioselective approach to substituted pyridazine *N*-oxides, is reported in this paper.

The first objective of our investigation was to establish a route to scaffold **6**. As alluded to above, direct oxidation of the corresponding pyridazines was problematic. In our hands, this strategy generated both *N*-oxide regioisomers. To circumvent this obstacle, we focused instead on executing site-selective reactions on 3,6-dichloropyridazine *N*-oxide.[10] Noncatalyzed S$_N$Ar reactions of this heterocycle are known; however, regioselectivities are modest, and site-selectivity is dependent on the structure of the nucleophile.[11] Alternatively, selective cross-coupling reactions of polychlorinated diazines have been described by Hu, Villemin, and Buchwald.[12,13] Inspired by these studies, we envisioned using a two-stage process to convert 3,6-dichloropyridazine *N*-oxide to **6**. Accordingly, a regioselective Pd-catalyzed Suzuki reaction

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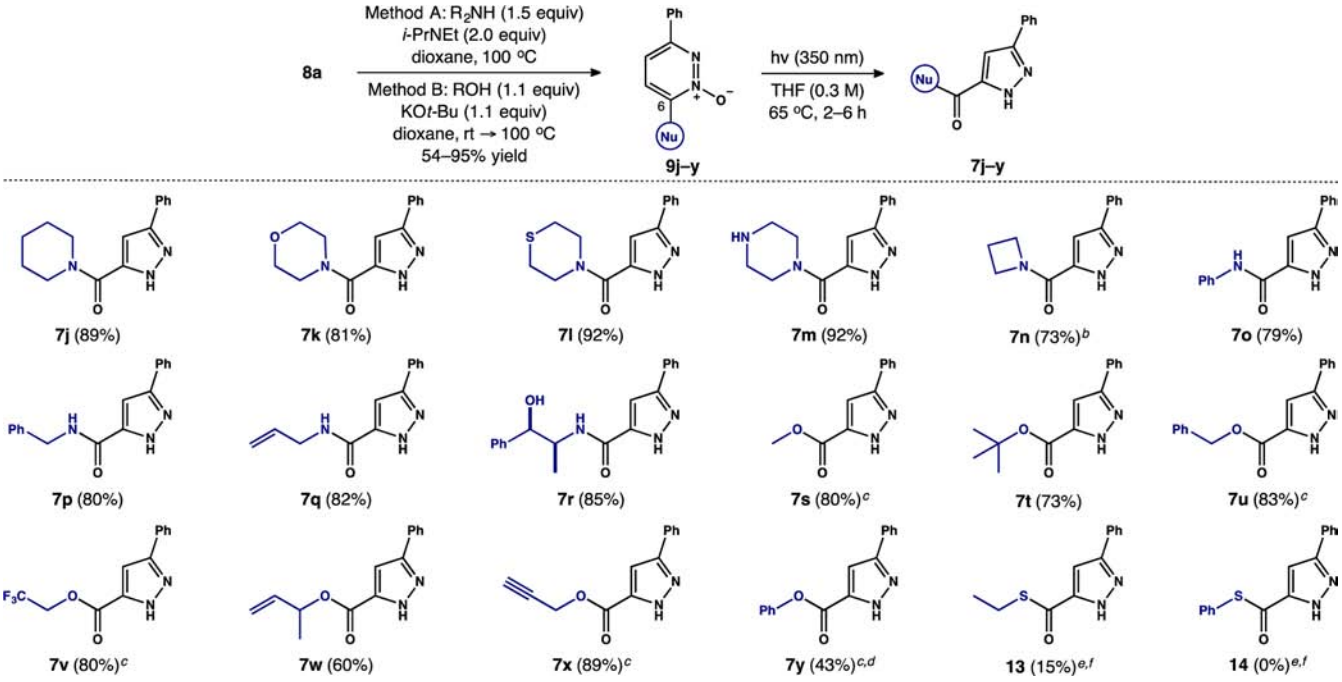
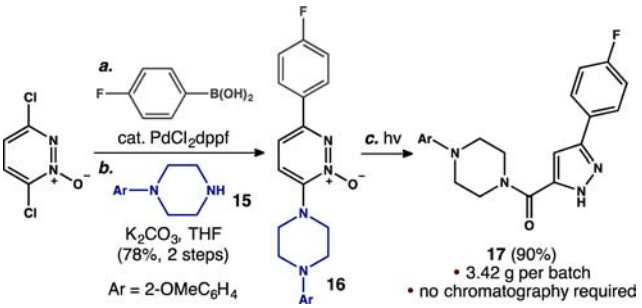
Scheme 3. Scope of Heteroatom Groups at the C6 Position[a]



[a]Isolated yields are reported and are an average of two experiments. [b]19% of furan side product was observed. [c]Furan side product was formed in 5–9% yield. [d]Photodeoxygenation was observed. [e]Irradiated at 350 nm for 14 h. [f]The mass balance was starting material.

Scheme 4. Multigram-Scale Synthesis of hNK$_3$ Receptor Antagonist 17[a]



[a]Reagents and conditions: (a) 4-fluorophenylboronic acid (1.1 equiv), 2 M aq K_3PO_4, $PdCl_2$dppf (5 mol %), THF (0.3 M), 65 °C, 2 h, 85%; (b) **15** (2.0 equiv), K_2CO_3 (3.0 equiv), THF (0.3 M), 65 °C, 24 h, 92%; (c) hν (350 nm), THF (0.3 M), 65 °C, 5 h, 90%.

would first be used to install the desired aryl group, thereby allowing a range of heteroatom nucleophiles to be added in a second operation.

With this strategy in mind, we set out to identify a catalyst system capable of discriminating between the two aryl−chloride bonds in 3,6-dichloropyridazine *N*-oxide. Using 1.1 equiv of phenylboronic acid as a cross-coupling partner, we screened Pd/phosphine ligand combinations reported for Suzuki reactions of nitrogen heterocycles.[14,15] The majority of catalyst systems we tested provided undesired mixtures of C3-arylated product **8a** and **1**. The exception was $PdCl_2$dppf, which furnished **8a** as the main product.[16] After further exploration of the reaction parameters, we determined that catalytic $PdCl_2$dppf (3 mol %) in combination with aq K_3PO_4 and THF afforded **8a** in 93% yield (Table 1, entry 1).[17]

As illustrated in Table 1, this protocol was compatible with a range of arylboronic acids. Thus, 3,6-dichloropyridazine *N*-oxide reacted with unactivated and electron-rich arenes to selectively afford C3-arylated products **8a**−**e** in excellent yield (entries 1−5). Higher catalyst loading (5 mol %) was needed to achieve good yields using electron-deficient boronic acids (entries 6 and 7). Nitrogen-containing partners also reacted slowly, although good yields of **8h**−**i** were obtained using 5 mol % of $PdCl_2$dppf in dioxane at 95 °C (entries 8 and 9). Notably, the C6-arylated isomer of **8** was not detected in these reactions.

Having reduced to practice a robust synthesis of 3-aryl-5-chloropyridazine *N*-oxides (**8**), we were positioned to test our central hypothesis. Accordingly, **8a** was reacted with pyrrolidine and K_2CO_3 in THF at 65 °C to furnish 3-phenyl-6-pyrrolidinylpyridazine *N*-oxide (**9a**) in 94% yield.[18] To our delight, photolysis of **9a** did not result in deoxygenation. Instead, pyrazole **7a** was cleanly formed along with minor amounts of furan **11** and allene **12**. Consistent with the mechanism in Scheme 1, these photoproducts are generated from diazo intermediate **10**, a reactive species we observed by NMR but could not isolate.[19] Thus, **11** and **12** likely arise via a competing carbene pathway from decomposition of **10** (e.g., **A** → **2**, Scheme 1). Upon further experimentation, we found that these side products were virtually eliminated by exposing a solution of **9a** in THF (0.3 M) to 350 nm UV light at 65 °C for 2 h. This optimized protocol furnished **7a** in 93% yield.

Salient results from our optimization studies are summarized in Table 2. UV light was found to be essential to the reaction (entry 2). In general, increasing the reaction temperature from 35 to 65 °C was required to promote formation of **7a** relative to **11** and **12** (entry 3). THF was the most versatile solvent for this reaction; however, excellent results were achieved by irradiating more dilute solutions of **9a** (0.1 M) in MeOH, MeCN, or dioxane (entries 6−10). Conversely, CH_2Cl_2 was incompatible with this chemistry (entry 11). We also obtained inferior results using shorter wavelength UV light (entries 12 and 13). Importantly,

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these reactions were carried out under ambient atmosphere using untreated solvents and inexpensive borosilicate glassware.

With optimized reaction conditions in hand, the initial scope of the photoinduced isomerization reaction was explored. In general, the composition of the aryl substituent had little impact on the reaction outcome (Scheme 2). Sterically demanding substituents (**7c**) as well as both electron-rich (**7d** and **7e**) and electron-deficient (**7f**, and **7g**) arenes were equally well tolerated in the reaction. Moreover, *N*-oxides containing basic nitrogen functional groups afforded excellent yields of the corresponding pyrazoles (**7h** and **7i**). Taken together, these results indicate that inductive effects of C3-aryl groups are muted when a heteroatom substituent is present in structure **9**.

We also investigated the scope of C6 heteroatom groups in the photoreaction. As illustrated in Scheme 3, a family of pyridazine *N*-oxides (**9j**–**y**) was prepared by reacting **8a** with nitrogen, oxygen, and sulfur nucleophiles. When reacted under optimal photochemical conditions, a range of tertiary and secondary amines were well tolerated (**7j**–**r**), including those containing sulfur (**7l**) and both unprotected amine (**7m**) and alcohol (**7r**) functional groups. Azetidine (**7n**) and aniline (**7o**) derivatives were also compatible with this chemistry. Similarly, photosubstrates **9s**–**y** containing aryl ethers reacted smoothly to give the corresponding pyrazole esters **7s**–**x** in 60–89% yield. The lone exception in this group was phenol derivative **9y**, which afforded pyrazole **7y** in 43% yield along with the parent pyridazine derived from photodeoxygenation. Notably, pyridazine *N*-oxides harboring sulfur groups at C6 failed to react to any appreciable extent.

To highlight the synthetic utility of this method, we aimed to apply our strategy to the synthesis of a drug-type molecule. Toward this end, we became aware of a report by Cephalon that identified 3-aryl-5-acylpiperazinyl pyrazoles as potent antagonists of the G protein-coupled human tachykinin NK_3 receptor.[9a] The pharmacology of this scaffold reportedly mimics that of osanetant, a compound evaluated in human clinical trials by Sanofi for the treatment of schizophrenia.

A three-step synthesis of hNK_3 antagonist **17** (IC_{50} = 240 nM) is described in Scheme 4. Accordingly, a large-scale (20.0 mmol) cross coupling of 3,6-dichloropyridazine *N*-oxide and 4-fluorophenylboronic acid furnished **8f** in 85% yield. Subsequent amidation of **8f** with piperazine **15** generated photosubstrate **16** in 92% yield. Photolysis of **16** (THF, 0.3 M) smoothly afforded pyrazole **17** in high yield after 5 h. When carried out on 10.0 mmol scale, this reaction produced 3.42 g of **17** (90% yield) as a crystalline solid.

In summary, we have developed a distinct photochemical reaction for the synthesis of pyrazoles. This approach highlights the utility of photoinduced ring-opening reactions of pyridazine *N*-oxides for the first time. In contrast to existing methods,[8] the photochemistry described here offers a scalable, modular, and exceedingly mild way to prepare 3-aryl-5-acyl-1*H*-pyrazoles. Efforts to adapt this chemistry to continuous flow and further apply the photochemical ring opening of 1,2-diazine *N*-oxides to complex synthetic targets are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02562.

Optimization data, detailed synthetic procedures, characterization data, and ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(15) See the Supporting Information for more details.
(16) Regiochemistry of **8a** and **9a** was confirmed by X-ray crystallography. These data have been deposited at the Cambridge Structural Database as entries 1500539 (**8a**) and 1500541 (**9a**). The regiochemistry of **8b**–**i** was inferred by formation of the pyrazoles **7b**–**i**.
(17) Resubmission of **8a** to these reaction conditions afforded **1** quantitatively after 3 h. Thus, we speculate that the *N*-oxide group, together with use of the bulky ferrocene ligand, directs the reaction to the C3 position via combined steric effects.
(18) Compound **9a** exhibited strong absorbance bands at 275 nm ($\pi \rightarrow \pi^*$) and 358 ($n \rightarrow \pi^*$). See the Supporting Information for UV–vis data.
(19) An NMR experiment following the thermal conversion of **10** and to **7a** is available in the Supporting Information.

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