

# Dual Nickel- and Photoredox-Catalyzed Reductive Cross-Coupling to Access Chiral Trifluoromethylated Alkanes

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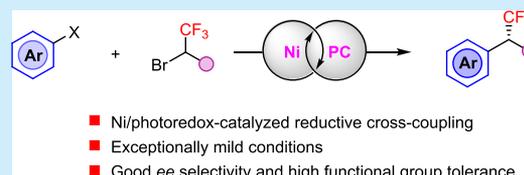


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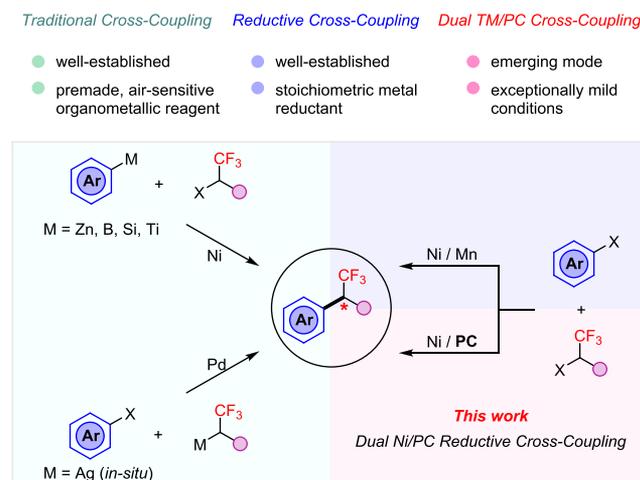
Supporting Information

**ABSTRACT:** A dual nickel/photoredox-catalyzed enantioselective reductive cross-coupling of aryl halides with CF<sub>3</sub>-substituted racemic alkyl electrophiles has been established. The approach accommodates a broad palette of aryl iodides and alkyl bromides to access a variety of chiral CF<sub>3</sub>-containing compounds. The exceptionally mild conditions (visible light, ambient temperature, no strong base) and no need for Grignard reagents or stoichiometric metallic reductants provide this transformation huge potential in the application of the late-stage functionalization of complex molecules.



Given that the incorporation of the trifluoromethyl (CF<sub>3</sub>) group into biologically active molecules in pharmaceutical and agricultural chemistry has a significant effect on their properties,<sup>1</sup> the exploration of trifluoromethylation reactions, especially on the construction of chiral structures containing C–CF<sub>3</sub> bonds, has drawn much attention.<sup>2</sup> Although many achievements in asymmetric nucleophilic or electrophilic trifluoromethylations have been made during the last several decades, transition-metal-catalyzed cross-couplings of CF<sub>3</sub>-substituted electrophiles with organometallic reagents also represent one of the highly efficient and straightforward routes (Scheme 1).<sup>3</sup> Among them, arylzinc,<sup>4</sup> arylboronic,<sup>5</sup> arylsilyl,<sup>6</sup> and aryltitanic<sup>7</sup> reagents have been employed in succession as partners with CF<sub>3</sub>-containing alkyl halides or pseudohalides

## Scheme 1. Asymmetric Cross-Couplings to Access the Chiral Benzylic CF<sub>3</sub> Molecules<sup>a</sup>



<sup>a</sup>TM, transition-metal. PC, photoredox catalyst.

using nickel catalysis to generate the benzylic chiral C–CF<sub>3</sub> bond. In addition, an enantioselective palladium-catalyzed coupling of aryl halides with an in-situ-generated  $\alpha$ -trifluoromethylated alkylsilver species was reported by Zhang's group to deliver chiral CF<sub>3</sub>-bearing molecules.<sup>8</sup> Despite these advances, these works usually focused on the pre-made or in-situ-formed air-sensitive organometallic reagents, thus commonly limiting the substrate scopes and the functional group tolerance. To address these issues, the reductive cross-coupling of two easily available electrophiles would provide a convenient route.<sup>9</sup> As part of our ongoing research interest in the dual Ni/photoredox-catalyzed reductive cross-coupling (RCC) reactions,<sup>10</sup> we speculated if this mild condition could be applied in this chiral C–CF<sub>3</sub> bond construction. Very recently, when this work was almost finished, the Wang group reported an elegant asymmetric RCC trifluoroalkylation of aryl iodides.<sup>11</sup> However, this approach still relied on the use of stoichiometric amounts of manganese reductant to compete for the catalytic cycle. Thus efforts toward exploring alternative reducing agents and novel catalytic systems are still highly beneficial to broaden the utility of this RCC reaction.

Visible-light-induced photoredox catalysis has been proven to be a powerful tool in methodology development and organic synthesis.<sup>12</sup> In the past decade, the combination of photoredox catalysis and transition-metal catalysts, termed as “metal-photoredox”,<sup>13</sup> has been an emerging mode to construct carbon–carbon bonds and carbon–heteroatom bonds that were unfeasible or difficult to achieve with a single catalytic

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system.<sup>14</sup> Although a number of asymmetric studies on such a cooperative regime have been developed upon the cross-couplings, especially with nickel, they are largely limited to redox-neutral reactions.<sup>15</sup> The dual nickel/photoredox-catalyzed asymmetric reductive cross-coupling is still much less observed.<sup>16</sup> Recently, by this strategy, we demonstrated an enantioselective RCC of aryl iodides with  $\alpha$ -chloroboranes under exceptionally mild conditions.<sup>10b</sup> Herein we would like to facilitate this route further to create chiral CF<sub>3</sub>-bearing molecules.

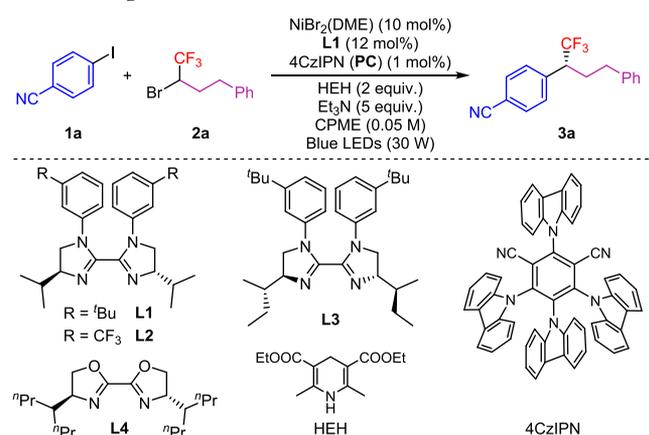
Initial exploration into this dual Ni/photoredox-catalyzed process focused on using **1a** as the sp<sub>2</sub>-hybridized electrophile and racemic CF<sub>3</sub>-containing precursor **2a** as another partner. After a systematic evaluation of all of the reaction parameters, product **3a** was concertedly afforded in high yield with good enantioselectivity under the conditions listed in entry 1 of Table 1. The change of nickel catalyst to Ni(cod)<sub>2</sub> or NiI<sub>2</sub> led to a lower yield but had no distinct influence on the enantioselectivity (entries 2 and 3, Table 1). The ligand with CF<sub>3</sub> substitution on the aryl group (**L2**) gave only the product with a decreased yield, highlighting the importance of the electron property of the ligand (entry 4, Table 1). A higher

yield was observed but a lower enantioselectivity was given with a dual chiral center ligand **L3**, whereas the popular bis(oxazolines) ligand **L4** afforded the benzyl CF<sub>3</sub> product in an obviously diminished yield (entries 5 and 6, Table 1). Other photoredox catalysts only gave lower conversions (entries 7 and 8, Table 1). The further examination of several solvents confirmed the best outcome with CPME (entries 9 and 10, Table 1). The same conclusion regarding the Et<sub>3</sub>N selection was also deduced after systematic tests with organic or inorganic bases (entries 11 and 12, Table 1). Control experiments in the absence of Hantzsch ester (HEH), Et<sub>3</sub>N, nickel catalyst, photoredox 4CzIPN, or light resulted in no detectable product formation (entries 13 and 14, Table 1), strengthening the essential role of each of these components in this asymmetric reductive cross-coupling process.

With the optimized conditions in hand, we investigated the scopes of this dual nickel/photoredox-catalyzed reductive cross-coupling (Scheme 2). In general, the aryl iodides with either electron-donating or electron-withdrawing functional groups on the meta and para positions can react smoothly to give the corresponding products in moderate to high yields with good enantioselectivities. The aryl bromide can also be utilized as a partner to give the product in the same enantiomer ratio and a bit lower yield (**3a**). A variety of versatile functional groups that have great potential in the further transformation, such as nitrile (**3a**), ester (**3b**), aldehyde (**3c**), and ketone (**3d**, **3e**), were well tolerated in this RCC process. The sulfur-containing group including thioether (**3f**) and sulfone (**3g**) in the benzene ring did not influence the high yields and enantioselectivities. The aryl iodides bearing an ether on the para position could give the corresponding product without a significant reduction in yield but a decreased *er* value (**3h**), thus giving some insights into the electronic effect on this transformation. In addition, the substrates processing a meta substituent (**3i–3l**) as well as the multiple substituted candidates (**3m**, **3n**) can be employed to afford the chiral CF<sub>3</sub>-containing products in undiminished yields and selectivity. When moving to the heterocyclic iodides, in an effort to showcase the mild nature of this method, the reactions still readily proceeded under the optimized conditions (**3o**, **3p**). Then, the method was applied to the  $\alpha$ -trifluoromethyl bromides for a further study of the scope of this dual-catalytic regime (**3q–3z**). Identically, a diverse set of functional groups, including ester (**3q**, **3r**, **3u**), amide (**3s**), alcohol (**3t**), alkyl (**3v**), ether (**3w**), protected phenol (**3x**), thiazole (**3y**), and ferrocene (**3z**), were tolerated. These results serve to highlight the broad scope and high chemoselectivity of the current method.

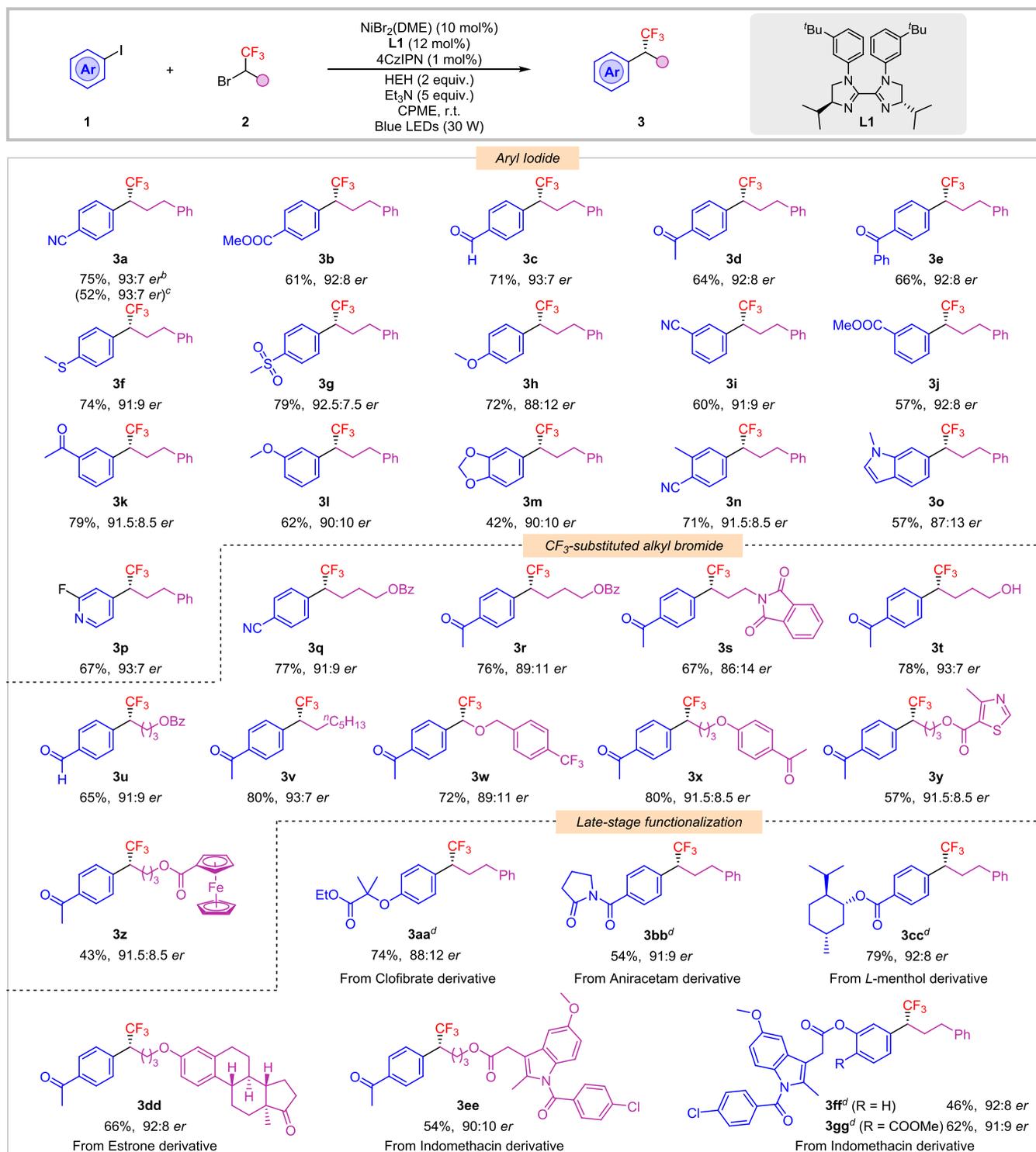
To further illustrate the utility of this method, this dual nickel/photoredox-catalyzed reductive cross-coupling was applied for the rapid, late-stage modification of natural products and drug molecules, which typically requires mild reaction conditions and high functional-group tolerance. Aryl iodides derived from drugs such as clofibrate (**3aa**) and aniracetam (**3bb**) were transformed into the corresponding chiral CF<sub>3</sub>-containing products with this strategy. The alkyl bromides or aryl iodides bearing multiple stereocenters, such as **3cc**, a chiral *L*-menthol derivative, and **3dd**, a steroidal framework, were all amenable for this process. In addition, the components (**3ee–3gg**) with an indomethacin skeleton underwent smooth transformations as well. The successful late-stage functionalization of these natural products and drugs, many of which contain sensitive ester, amide, aryl chloride, and

Table 1. Optimization Conditions<sup>a</sup>



entry	changes	yield (%)	<i>er</i>
1	no change	82 <sup>b</sup>	93:7
2	using Ni(cod) <sub>2</sub>	45	93:7
3	using NiI <sub>2</sub>	50	91:9
4	<b>L2</b> instead of <b>L1</b>	6	88.5:11.5
5	<b>L3</b> instead of <b>L1</b>	98	91:9
6	<b>L4</b> instead of <b>L1</b>	38	95:5
7	[Ir(dFCF <sub>3</sub> ppy)dtbbpy]PF <sub>6</sub> as PC	46	93:7
8	Ru(bpy) <sub>3</sub> Cl <sub>2</sub> ·6H <sub>2</sub> O as PC	n.d.	
9	TBME as solvent	82	92.5:7.5
10	DMA as solvent	20	94:6
11	DIPEA instead of Et <sub>3</sub> N	14	92.5:7.5
12	Na <sub>2</sub> CO <sub>3</sub> instead of Et <sub>3</sub> N	n.d.	
13	no HEH/Et <sub>3</sub> N	n.d.	
14	no Ni/4CzIPN/light	n.d.	

<sup>a</sup>Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), NiBr<sub>2</sub>(DME) (10 mol %), **L1** (12 mol %), 4CzIPN (1 mol %), HEH (2 equiv.), Et<sub>3</sub>N (5 equiv.), CPME (2 mL), blue LED lamp (30 W), room temperature, 8–10 h. The yields were determined by GC with <sup>n</sup>dodecane as an internal standard. The enantiomer ratio (*er*) values were determined by HPLC. <sup>b</sup>75% isolated yield. CPME, cyclopentyl methyl ether. TBME, <sup>t</sup>butyl methyl ether. DIPEA, *N,N*-diisopropylethylamine.

Scheme 2. Scopes of Dual Ni/Photoredox-Catalyzed Reductive Cross-Coupling<sup>a</sup>

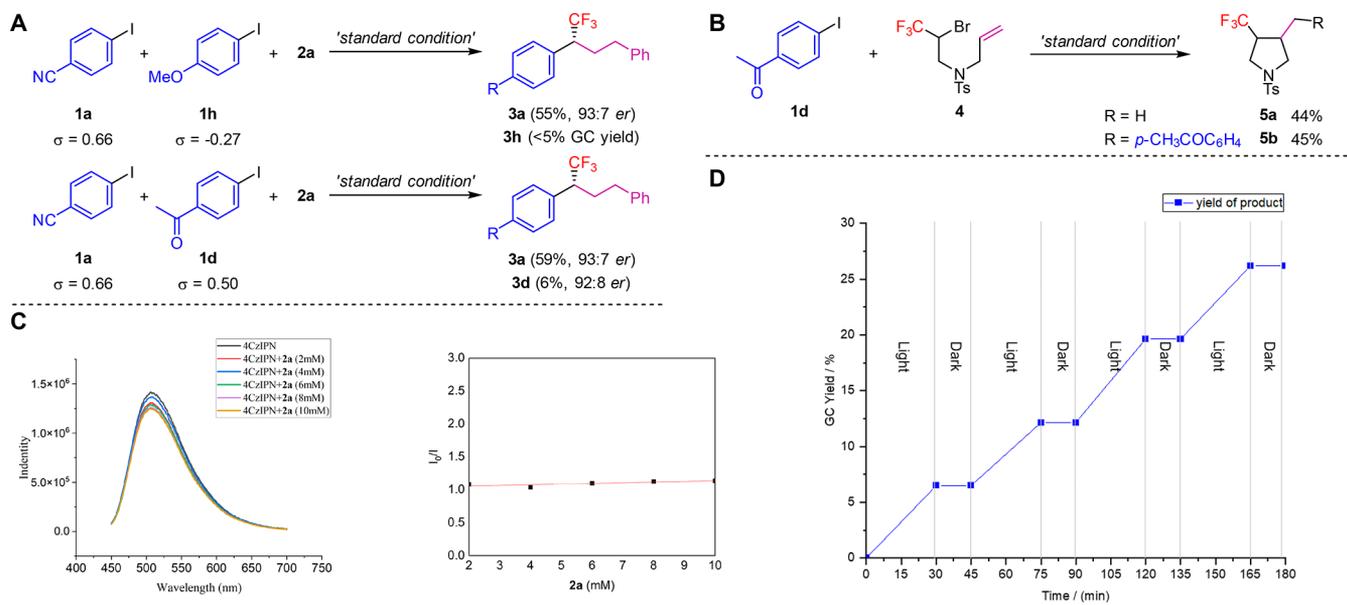
<sup>a</sup>Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol), NiBr<sub>2</sub>(DME) (10 mol %), L1 (12 mol %), 4CzIPN (1 mol %), HEH (2 equiv), Et<sub>3</sub>N (5 equiv), CPME (4 mL), blue LED lamp (30 W), room temperature, 8–10 h. Isolated yields are given. The *er* values were determined by HPLC. <sup>b</sup>Reaction on a 1 mmol scale gave the product in 68% yield (93:7 *er*). <sup>c</sup>4-Bromobenzonitrile was utilized. <sup>d</sup>Compounds **1** (0.2 mmol) and **2** (0.3 mmol) were used.

heterocyclic groups, underscores the high potential of this methodology in the late-stage functionalization of complex molecules.

To give some insights into the features and mechanism of the coupling, we performed some experiments. Although both

electron-rich and electron-poor aryl iodides can be employed in this transformation, the substrates with electron-withdrawing groups take overwhelming precedence over the ones with richer electronic properties, as evidenced by the competing reaction with **1a** (*para*-CN,  $\sigma = 0.66$ ) and **1h**

## Scheme 3. Competition Experiments and Mechanistic Studies



(*para*-OMe,  $\sigma = -0.27$ ). Even for the two competitors with very close electronic densities, such as **1a** (*para*-CN,  $\sigma = 0.66$ ) and **1d** (*para*-Ac,  $\sigma = 0.50$ ), the selectivity was still very high, thus illustrating the strong influence on the oxidative addition step from the component electronic property in this process (Scheme 3A). Moreover, when the reaction was conducted in the presence of 2 equiv of 2,2,6,6-tetramethylpiperidinoxy (TEMPO), the product was obtained in only 12% yield, which was much lower than that observed under the standard conditions. When compound **4** was treating with **1a** under the standard conditions, the ring cyclization products **5a** and **5b** were obtained in 44 and 45% yield, respectively, highly suggesting that a radical mechanism was probably involved in this scenario (Scheme 3B).

Meanwhile, the luminescence quenching experiment with substrate **2a** was investigated, and the results showed that it is unlikely to quench the excited state of 4CzIPN (Scheme 3C). Combined with our previous results,<sup>10b</sup> it is still possible that HEH is responsible for quenching the active state [4CzIPN]\*. In addition, the model reaction with **1a** and **2a** under the standard conditions was stirred for 3 h, alternating between 30 min periods of blue LED light irradiation and 15 min periods of a complete lack of light irradiation (Scheme 3D). It was observed that the reaction progressed steadily with blue LED light irradiation, but it abruptly stalled when the light source was removed, thus clearly showcasing the necessity and importance of the light irradiation in this dual catalysis system.

In summary, we have reported a dual nickel/photoredox-catalyzed regime to accomplish a wide array of enantioconvergent reductive cross-couplings of aryl halides with CF<sub>3</sub>-substituted racemic alkyl electrophiles. Compared with traditional strategies to construct this kind of enantiomerically enriched trifluoromethylated compound, the approach can proceed under very mild conditions and exhibits excellent catalytic efficiency. It accommodates a broad scope of many functional groups, thus highlighting the potential of this methodology in the late-stage functionalization of complex molecules.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c01420>.

Experimental procedures and spectroscopic data for new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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