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Bioinspired Selective Synthesis of Heterodimer 8−5′ or 8−*O*−4′ Neolignan Analogs

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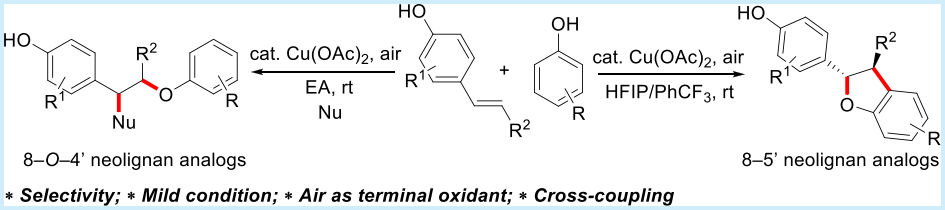
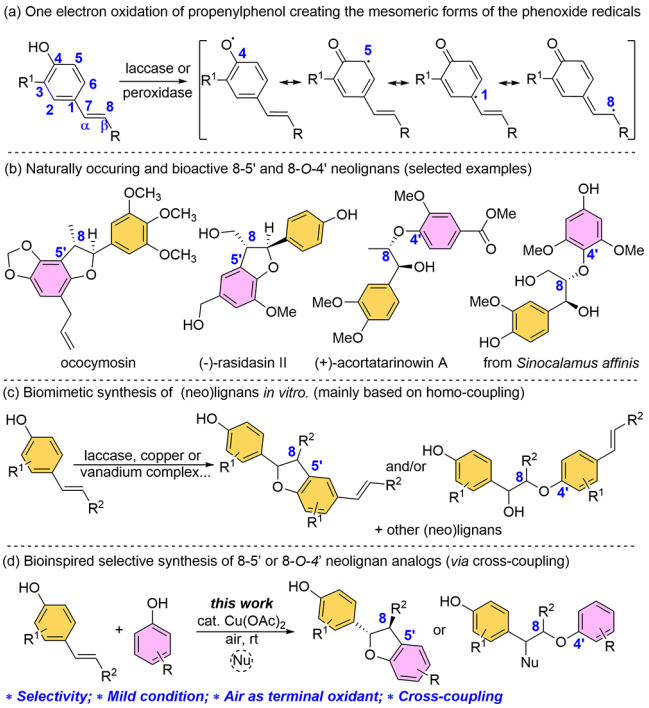


ABSTRACT: The bioinspired synthesis of heterodimer neolignan analogs is reported by single-electron oxidation of both alkenyl phenols and phenols individually, followed by a combination of the resultant radicals. This oxidative radical cross-coupling strategy can afford heterodimer 8−5′ or 8−*O*−4′ neolignan analogs selectively with the use of air as the terminal oxidant and copper acetate as the catalyst at room temperature.

Phenols are important motifs abundant in many natural products, pharmaceuticals, and agrochemicals. The high reactivity of phenol derivatives makes them versatile building blocks in both natural and synthetic contexts.[1] For example, by the actions of copper or iron containing laccases or peroxidases, the propenylphenol can form a radical intermediate stabilized by resonance according to the mesomeric forms shown in Scheme 1a, and radical couplings of these mesomeric forms can produce a variety of natural products such as lignins, lignans, neolignans, etc.[2] Lignans are naturally occurring phenols which are widespread within the plant kingdom.[3] Traditionally, they are classified into two types, viz. classical lignans and neolignans. Classical lignan refers to a dimer generated by 8−8′ oxidative coupling of two propenylphenols, whereas the neolignan refers to one formed by a coupling other than 8−8′.[4] Among the neolignans, those heterodimers with a dihydrobenzofuran (8−5′-coupling) or alkyl aryl ether (8−*O*−4′-coupling) core are worthy of particular attention for the wide range of their biological activities including antioxidant, anti-inflammatory, antiplasmodial, neuroprotective activities, anticancer, etc. (Scheme 1b).[5]

The biogenesis of these natural products has inspired a number of methodologies for the synthesis of dihydrobenzofuran and alkyl aryl ether neolignan derivatives *in vitro* (Scheme 1c).[6] For example, Chen reported *Rhus vernicifera* laccases catalyzed oxidation of isoeugenol and obtained the mixture of 8−5′-coupling dihydrobenzofuran dehydrodiisoeugenol and 8−*O*−4′-coupling alkyl aryl ether.[7] Tringali developed biomimetic synthesis of potent antiproliferative activity neolignanamides through laccase-mediated oxidative 8−5′-radical-coupling of hydroxycinnamoyl amides.[8] Lu studied copper(II)-tetramethylethylenediamine catalyzed bio-

Scheme 1. Synthesis of 8−5′ or 8−*O*−4′ Neolignan Analogs



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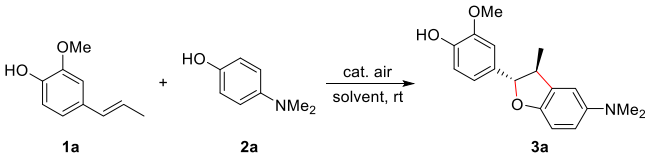
mimetic radical-coupling of ethyl ferulate, and the products are mixtures containing 8−*O*−4′, 8−5′, 8−8′, and 5−5′ coupled diferulates.[9] Recently, Kozlowski found that a vanadium complex can catalyze the oxidative homocoupling of 2,6-disubstituted terminal alkenyl phenols to synthesize *β*−*β* (8−8′) and *β*-O (8−*O*−4′) (neo)lignan analogs selectively.[10] In these studies, neolignan derivatives were prepared via homocoupling of propenylphenols, and the selective cross-coupling of alkenyl phenols with other partners is still unexplored.[11]

Although heterodimer neolignans are widespread in nature and could be considered biogenetically originating from different phenols, the selective phenol−phenol cross-coupling under oxidative conditions is difficult because of the multiple selectivity issues with two radical intermediates.[12] In most cases, the desired cross-couplings are generally accompanied by the homocouplings and nonselective couplings,[6a] thereby retarding efficient formation of the heterodimer neolignans. In continuation of our previous work on phenols couplings,[13] we sought to accomplish selective cross-coupling of alkenyl phenols and other phenol partners to afford heterodimer neolignan analogs. Considering that laccases are multicopper-containing oxidases that enable natural phenols to form various neolignans via aerobic oxidation,[2c] we turned our attention to the combination of copper catalyst and aerobic oxidation (Scheme 1d).[14]

Our initial investigation focused on the $Cu(OAc)_2$ (8 mol %) catalyzed cross-coupling of easily available isoeugenol **1a** (0.22 mmol) with 4-(dimethylamino)phenol **2a** (0.2 mmol) under air at room temperature. After extensive screening of various solvents (Table 1, entries 1−7), we were pleased to find that a 5:1 solvent mixture of trifluorotoluene ($PhCF_3$) and hexafluoroisopropanol (HFIP) afforded the desired 8−5′ neolignan analog **3a** in excellent yield (Table 1, entry 6, 93% yield). Moreover, replacing $Cu(OAc)_2$ with $CuSO_4$ only provided trace product. It was found that a comparable yield was obtained when $FeCl_3$ was used as the catalyst (entry 10), while the employment of CuCl led to a decreased yield (entry 9). The control experiments showed that air is necessary for the desired reaction (Table 1, entry 11). Moreover, the reaction run without $Cu(OAc)_2$ in the presence of air showed no product formation, indicating that the catalyst is key in oxidizing the substrates (Table 1, entry 12).

Table 1. Optimization of the Reactions Conditions[a]



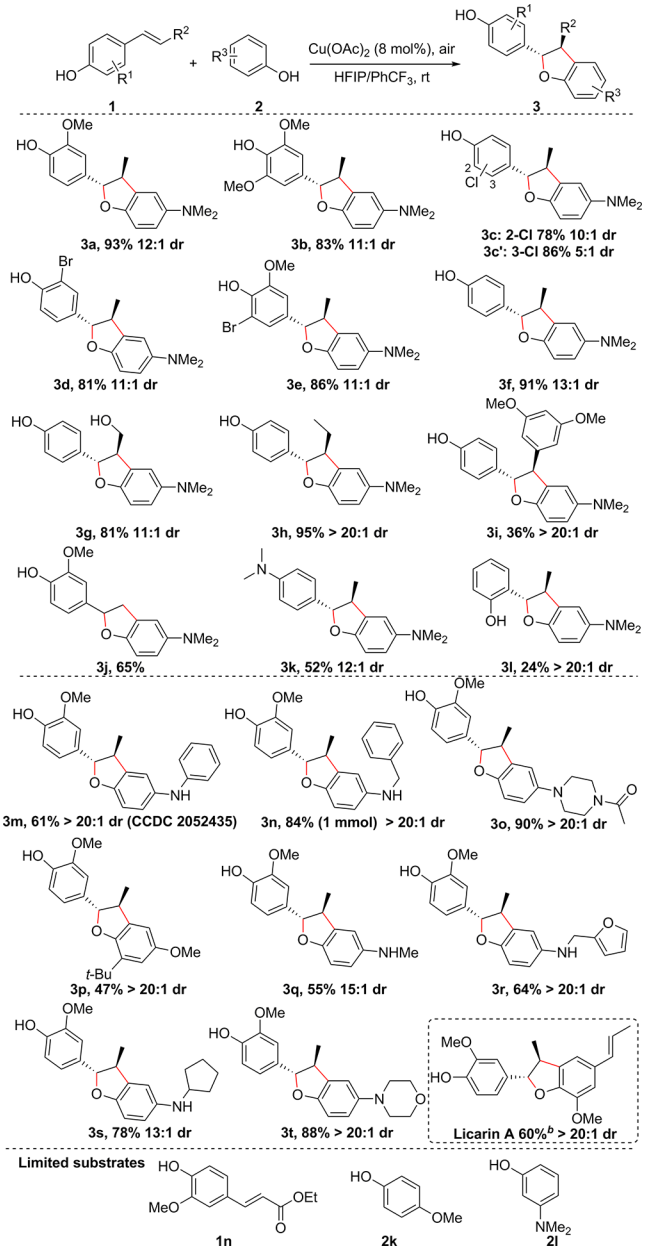
1a 2a 3a

entry	cat.	solvent[b]	yield (%)	dr[c]
1	$Cu(OAc)_2$	EA	44 (20 h)	>20:1
2	$Cu(OAc)_2$	THF or CH_3CN	trace (12 h)	–
3	$Cu(OAc)_2$	DCM	54 (12 h)	>20:1
4	$Cu(OAc)_2$	HFIP	71 (12 h)	10:1
5	$Cu(OAc)_2$	$PhCF_3$	44 (12 h)	>20:1
6	**$Cu(OAc)_2$**	**HFIP/$PhCF_3$**	**93 (3 h)**	12:1
7	$Cu(OAc)_2$	MeOH	44 (12 h)	>20:1
8	$CuSO_4$	HFIP/$PhCF_3$	trace (12 h)	–
9	CuCl	HFIP/$PhCF_3$	66 (20 h)	12:1
10	$FeCl_3$	HFIP/$PhCF_3$	84 (12 h)	12:1
11[d]	$Cu(OAc)_2$	HFIP/$PhCF_3$	trace (20 h)	–
12	no	HFIP/$PhCF_3$	N.D. (12 h)	–

[a]Reaction conditions: **1a** (0.22 mmol), **2a** (0.2 mmol), and Cat. (8 mol %) were added in 2 mL of solvent under air at rt, 3−20 h. [b]HFIP/$PhCF_3$ (0.3/1.5 mL). EA (ethyl acetate); DCM (dichloromethane); THF (tetrahydrofuran). [c]The diastereomeric ratios were determined by ^1H NMR spectroscopic analysis. [d]Under Ar. N.D. = not detected.

Following our initial optimization studies, we began to evaluate the scope of the cross-coupling reactions for a range of alkenyl phenols and electron-rich phenols. As shown in Scheme 2, a variety of *para*-alkenyl phenols bearing different aromatic substituent groups such as methoxyl (**3a**, **3b**), chloro (**3c**, **3c′**), and bromo (**3d**, **3e**) afforded the corresponding 8−

Scheme 2. Scope for Synthesis of 8−5′ Neolignan Analogs[a]



[a]Reaction conditions: **1** (0.22 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (8 mol %) were added in 1.8 mL of HFIP/$PhCF_3$ (0.3/1.5 mL) under air at rt, 3−12 h. [b]Without **2**.

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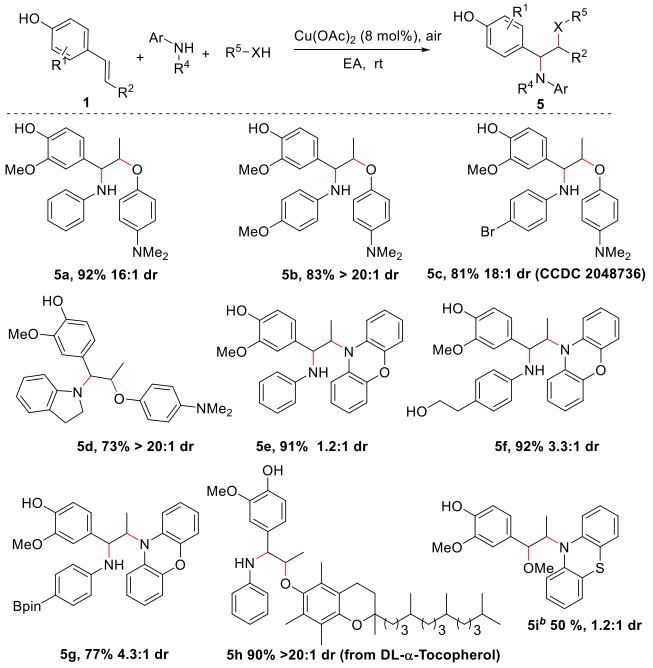
5′ neolignan analogs in good to excellent yields. The unsubstituted precursor was also oxidized in good yield to its corresponding cyclized product (**3f**). *para*-Coumaryl alcohol, one of the phenylpropenoid monolignol units of lignin, was suitable for producing **3g** in 81% yield. The alkenyl phenol bearing an ethyl group in the β position exhibited high reactivity (**3h**). Pterostilbene, a dimethyl ether derivative of resveratrol, could afford adduct **3i** in 36% yield. A terminal alkene worked well to generate the expected **3j** in good yield. Interestingly, *N*,*N*-dimethyl-4-(prop-1-en-1-yl)aniline was also a useful substrate to give product **3k** in moderate yield due to its formation of a resonance-stabilized free radical intermediate. *ortho*-Alkenyl phenols substrate was also found to be suitable for the reaction to afford the expected product **3l** albeit with less efficiency. The nonreactivity of **1n** may attribute to its high oxidant potential ($E_{p/2}^{ox}$ = 1.23 V vs Ag/AgCl; see the Supporting Information).

Encouraged by the above results, we next switched our attention to investigate the scope of electron-rich phenols. Various *N*-substituted 4-aminophenols (**3m**−**3o**, **3q**−**3t**) were well accommodated. Unfortunately, 4-methoxyphenol **2k** ($E_{p/2}^{ox}$ = 1.06 V vs Ag/AgCl) failed to participate in this reaction most likely due to the inferior efficiency for the single-electron oxidation to generate the phenol radical intermediate. Remarkably, the presence of an additional *tert*-butyl group at 4-methoxyphenol afforded product **3p** in 47% yield. 3-(Dimethylamino)phenol **2l** ($E_{p/2}^{ox}$ = 0.58 V vs Ag/AgCl) has a low oxidant potential but failed to give the product, probably due to its non-formation of a resonance-stabilized phenol radical compared with **2a** ($E_{p/2}^{ox}$ = 0.38 V vs Ag/AgCl). Interestingly, without **2a** present, dimerization product Licarin A was isolated in 60% yield. This suggests that the cross-coupling between **1a** and **2a** proceeds much faster than the homocoupling of **1a** under the standard reaction conditions.

It was found that 8−*O*−4′ neolignan analog **5a** could be produced dominantly instead of 8−5′ coupling **3a** when nucleophile aniline[15] was introduced into our copper(II)/air catalyst system (Table S1). An increased yield was observed (92%, dr = 16:1) when ethyl acetate (EA) was used as the solvent. With the optimized conditions in hand, we directed our studies toward exploring the scope of this three-component radical cross-coupling reaction. This effective method exhibits good tolerance of a broad range of functional groups. When using various anilines as nucleophiles, diverse functionalized products could be achieved via the copper-catalyzed aerobic coupling (**5a**−**5g**) (Scheme 3). The late-stage modification of DL-α-Tocopherol was also feasible to give the 8−*O*−4′ neolignan analog **5h** in 90% yield. Moreover, we found that phenoxazine as well as phenothiazine could also take part in the three-component cross-coupling (**5e**−**5g** and **5i**). Other nucleophiles such as MeOH were also efficient in this process, which afforded the corresponding adduct **5i** in 50% yield.

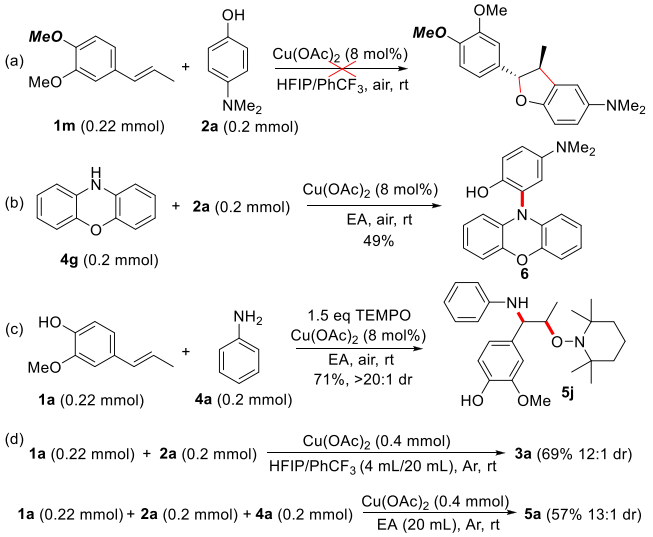
To gain some insight into the reaction process, we carried out a series of mechanistic studies. Methyl isoeugenol **1m** ($E_{p/2}^{ox}$ = 0.97 V vs Ag/AgCl) failed to give product, although the oxidant potential of **1m** is comparable to isoeugenol **1a** ($E_{p/2}^{ox}$ = 0.95 V vs Ag/AgCl), indicating that the phenolic OH group is crucial to substrate activation (Scheme 4a). The product **6** from **4g** and **2a** was achieved in our Cu/air catalyst system (Scheme 4b), probably via a radical cross-coupling process based on previous studies.[16] Thus, the radical cross-coupling pathway was likely involved, which was further

Scheme 3. Scope for Synthesis of 8−*O*−4′ Neolignan Analogs[a]



[a]Reaction conditions: **1** (0.22 mmol), **2**, phenoxazine or phenothiazine (0.2 mmol), anilines (0.2 mmol), $Cu(OAc)_2$ (8 mol %) were added in 2 mL EA under air at rt, 12−24 h. [b]MeOH as solvent.

Scheme 4. Control Experiments



supported by the radical trapping experiment with TEMPO to give adduct **5j** (Scheme 4c). Moreover, the desired products were still obtained in satisfactory yields with 2 equiv of $Cu(OAc)_2$ under Ar, suggesting that the oxygen might mainly function as the oxidant of the Cu(I) species (Scheme 4d).

Based on these results, a plausible mechanism is proposed in Scheme 5. The proposed pathway of these reactions features formation of Cu(II)-phenolates and subsequent single-electron transfer to afford phenoxyl radicals and cuprous species which could be oxidized to copper(II) by molecular oxygen. The key step of the reaction is the selective radical cross-coupling of **1a-II** with **2a-I** or **2a-II**. The formation of **3a** can be rationalized

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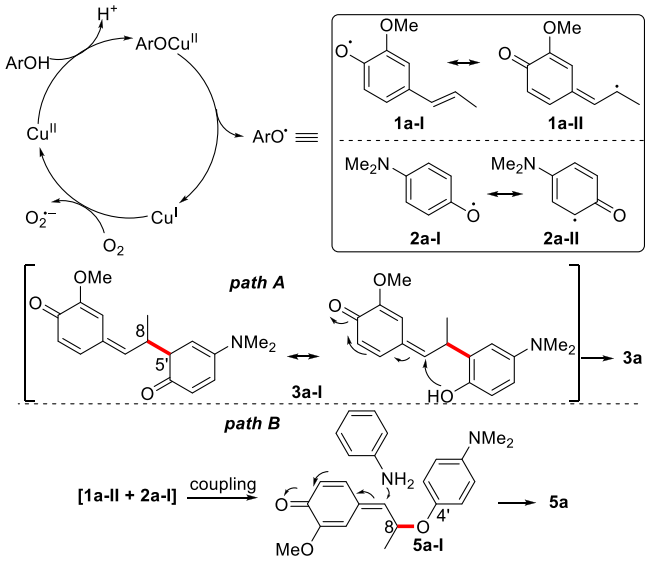
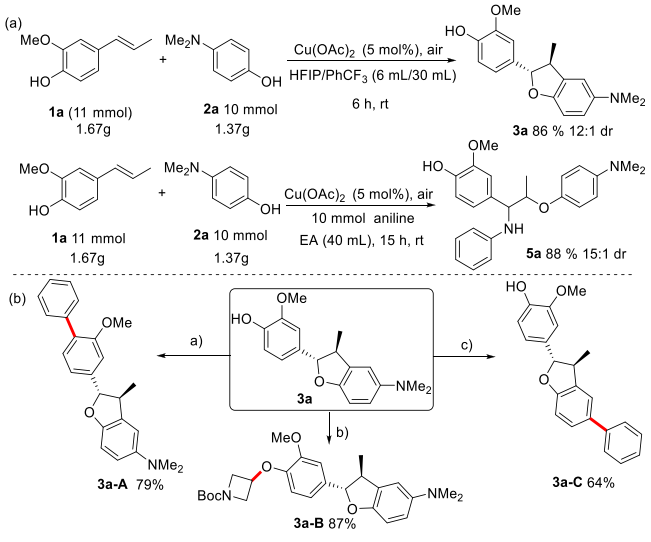
Scheme 5. Proposed Mechanisms



by the intramolecular nucleophilic addition of OH to quinone methide intermediate **3a-I** produced from the radical cross-coupling of **1a-II** with **2a-II**. Furthermore, the formation of **5a** can be rationalized by the intermolecular nucleophilic addition of aniline to quinone methide intermediate **5a-I** produced from the radical cross-coupling of **1a-II** with **2a-I**.

To demonstrate the practical application of these transformations in organic synthesis, we carried out gram-scale reactions as well as further functionalizations of the product **3a** (see the Supporting Information). First, a large-scale reaction of **1a** and **2a** was performed to deliver the desired product **3a** in 86% yield with 12:1 dr. Moreover, the desired product **5a** was obtained without a significant decrease in efficiency (88% versus 92%, Scheme 6a). As shown in Scheme 6b, **3a-A** was afforded in 79% yield by a two-step synthetic sequence involving Suzuki coupling. An alkylation sequence on **3a** delivered **3a-B** in 87% yield. **3a-C** can be afforded in 64% yield by a four-step synthetic sequence involving palladium-catalyzed cross-coupling of aryltrimethylammonium triflate with a Grignard reagent (Scheme 6b).[17]

Scheme 6. Gram-Scale Reactions and Applications of 3a to Diverse Scaffolds



[a](i) DMAP, Et_3N, Tf_2NPh, DCM; (ii) K_2CO_3, $Pd(PPh)_4$, PhB-$(OH)_2$, DMF, 90 °C. [b]$CsCO_3$, *tert*-butyl 3-iodoazetidine-1-carboxylate, MeCN, 80 °C. [c](i) AcCl, DIPEA, DCM, 0−25 °C; (ii) MeOTf, CH_2Cl_2; (iii) PhMgBr, $PdCl_2(PPh_3)_2$, THF; (iv) NaOH, MeOH.

In summary, we have developed a commercially available and earth-abundant Cu catalyst for the intermolecular oxidative cross-coupling reaction of alkenyl phenols and other coupling partners. The method proceeds under benign conditions, using O_2 in air as the oxidant at room temperature. More specifically, we demonstrate a regioselective oxidative cross-coupling for the direct construction of heterodimer 8−5′ or 8−*O*−4′ neolignan analogs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00762.

Experimental procedures, crystallographic data, compound characterization, and NMR spectra (PDF)

Accession Codes

CCDC 2048736 and 2052435 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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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