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Gold-Catalyzed Oxidative Cyclization Involving Nucleophilic Attack to the Keto Group of α,α′-Dioxo Gold Carbene and 1,2-Alkynyl Migration: Synthesis of Furan-3-carboxylates

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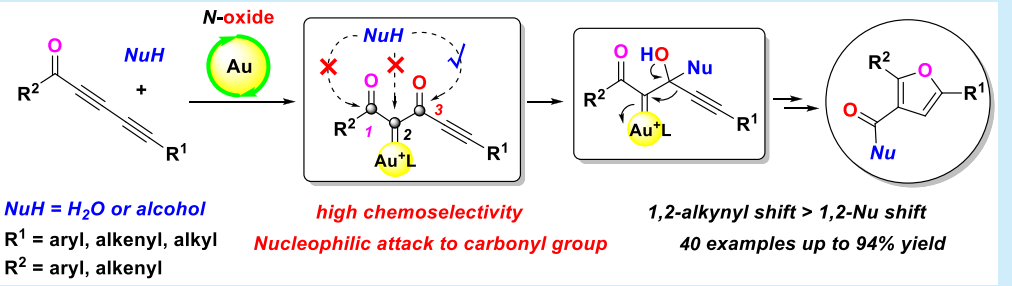

ABSTRACT: A multicomponent strategy for the synthesis of functionalized furan-3-carboxylates based on gold-catalyzed oxidative cyclization of diynones with alcohols or water has been developed. Mechanistic studies revealed that a rare nucleophilic attack to the carbonyl group of the α,α′-dioxo gold carbene instead of the carbene center and 1,2-alkynyl group migration were involved in this transformation. This method offers several advantages such as mild conditions, high regio- and chemoselectivity, and wide functional group compatibility.

The furan rings widely occur as key structural subunits in numerous natural products, pharmaceuticals, and flavor and fragrance compounds,[1] and they are also useful and versatile synthetic intermediates for access to heterocyclic and acyclic compounds.[2] Especially, substances containing a furan-3-carboxylate core display a broad range of pharmacological activities.[3] For example, dihydroxypyrrolidine-linked furan is a selective β-galactosidase inhibitor;[3a] S-linked fucosides show affinity toward E- and P-selectins;[3b] providencin displayed modest in vitro cytotoxicity against MCF7 breast cancer;[3c] and (+)-wortmannin is a potent PI3K inhibitor[3d] (Figure 1). While numerous strategies for the synthesis of furans have been developed, the efficient routes to furan-3-carboxylates are still limited. Frequently used methods for these compounds are direct functionalization of furan-3-carboxylates.[4] Recently, a variety of transition-metal-catalyzed reactions have emerged as convenient protocols,[5a−h] such as gold-catalyzed cycloisomerization of ester-bearing enynes[5a] or propargyl vinyl ethers,[5b] gold-catalyzed reactions of 1,3-dicarbonyl sulfonium ylides and alkynes,[5c] Pd-catalyzed oxidative cyclizations,[5d] Cu- or Co-catalyzed [3 + 2] cycloaddition of α-diazocarbonyls with enamines[5e] or alkynes,[5f,g] silver-mediated oxidative cyclization of 1,3-dicarbonyl compounds with terminal alkynes,[5h] etc.[5] However, these protocols usually suffer from the drawbacks such as narrow substrate scope, utilization of prefunctionalized acyclic compounds as the substrates, limited structure diversity of the products etc. Therefore, the development of novel and efficient approaches to furan-3-carboxylates with wide substrate scope and diverse substitution patterns from easily available building blocks is highly desirable.

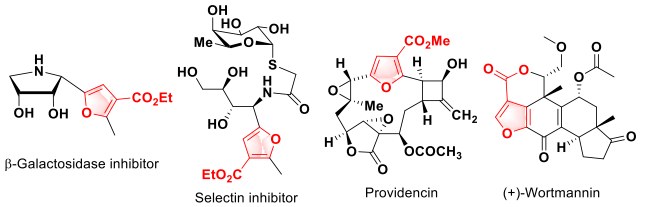

Figure 1. Typical examples of biologically active furan-3-carboxylates.

In recent years, gold-catalyzed oxygen transfer reactions using pyridine/quinoline *N*-oxides, sulfoxides, or nitrones as the oxidants have emerged as efficient methodologies for the construction of carbo- or heterocycles.[6] In most cases, the highly electrophilic α-oxo gold carbene intermediates are

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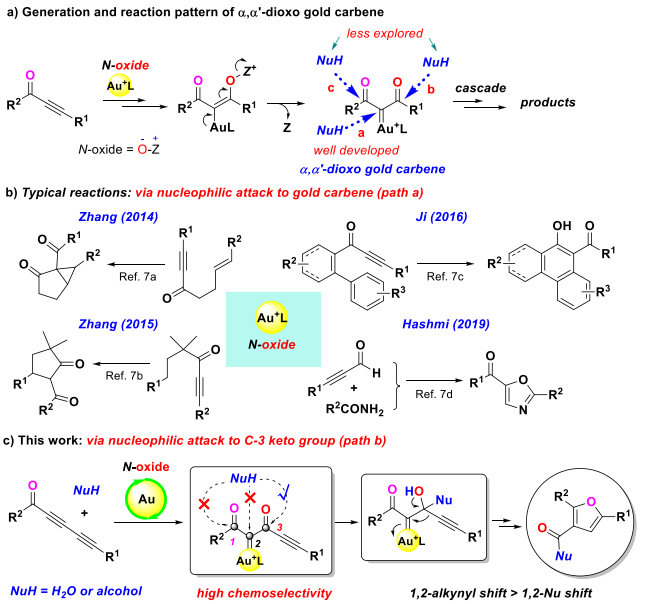
formed, which can be captured by nucleophiles to initiate the cascade reactions. A particularly attractive strategy for the generation of α,α'-dioxo gold carbenes is based on the use of ynones or propiolaldehydes as the substrates due to the enhanced electrophilicity and regioselectivity arising from the polarized triple bond (Scheme 1a). In principle, both of the

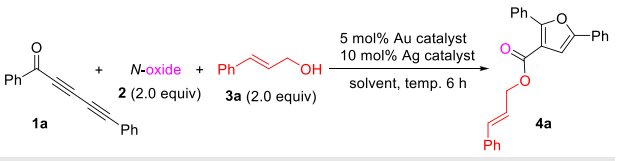
Scheme 1. Gold-Catalyzed Oxidative Reactions of Ynones

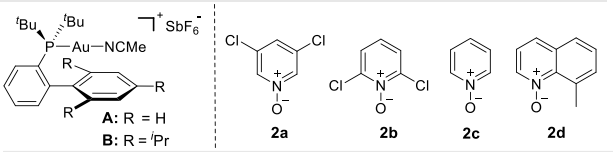


two keto groups and gold-carbene moiety can serve as an electrophilic center and would be attacked by a nucleophile. However, most of the reactions involve nucleophilic attack to gold carbenes (path a)[7] (Scheme 1b), and the selective attack to the keto groups remains a great challenge. During our ongoing project on gold-catalyzed reactions of ynones,[8,9] we envisioned that the use of diynones may have an important impact on the reaction pathways, which may allow the efficient attack of the nucleophile to the C-3 keto group (path b) due to the high reactivity and less steric hindrance of this site (Scheme 1c). Herein, we disclosed that the expected reactivity could be achieved using diynones as the substrates, enabling efficient access to furan-3-carboxylates or furan-3-carboxylic acids with wide structural diversity through gold-catalyzed oxidative cyclization of conjugated diynones with alcohols or water. Interestingly, a selective 1,2-alkynyl vs 1,2-Nu shift to gold carbene was also observed (Scheme 1c). It is noted that the intermolecular reactions of the gold carbene species with external nucleophiles are quite rare.[10]

The requisite diynones can be easily prepared by Cadiot–Chodkiewicz cross-coupling of propargyl alcohols with alkynyl bromide[11] followed by oxidation. To study the feasibility of the hypothesis, we initially investigated the gold-catalyzed oxidative reaction of 1,5-diphenylpenta-2,4-diyn-1-one **1a** using cinnamyl alcohol **3a** as the nucleophile in the presence of 3,5-dichloropyridine *N*-oxide **2a**. Gratifyingly, furan-3-carboxylate **4a** with blue fluorescence could be formed in 23% yield using 5 mol % of PPh_3AuNTf_2 as the catalyst in DCE at 80 °C for 6 h (Scheme 2, entry 1). The use of Johnphos Au(MeCN)SbF_6 (catalyst **A**) improved the yield of **4a** to 63% (entry 2). However, the use of a gold complex with a more crowded ligand such as ^{t}BuXphos (catalyst **B**) led to

Scheme 2. Optimization Studies





entry	Au catalyst	Ag catalyst	*N*-oxide	solvent	temp.	yield (%)[a]
1	PPh_3AuNTf_2	-	**2a**	DCE	80	23
2	**A**	-	**2a**	DCE	80	63
3	**B**	-	**2a**	DCE	80	20
4	$AuBr_3$	-	**2a**	DCE	80	9
5	$IPrAuNTf_2$	-	**2a**	DCE	80	77
6	IPrAuCl	$AgNTf_2$	**2a**	DCE	80	58
7	IPrAuCl	AgOTs	**2a**	DCE	80	65
8	IPrAuCl	$AgBF_4$	**2a**	DCE	80	52
9[b]	$IPrAuNTf_2$	-	**2a**	DCE	80	73
10	$IPrAuNTf_2$	-	**2a**	DCE	60	82
11	$IPrAuNTf_2$	-	**2b**	DCE	60	9%[c]
12	$IPrAuNTf_2$	-	**2c**	DCE	60	18%
13	$IPrAuNTf_2$	-	**2d**	DCE	60	22%[c]
14	$IPrAuNTf_2$	-	**2a**	MeCN	60	12
15	$IPrAuNTf_2$	-	**2a**	toluene	60	65
16	$IPrAuNTf_2$	-	**2a**	THF	60	4
17	-	-	**2a**	DCE	60	0
18	-	$AgNTf_2$	**2a**	DCE	60	0
19[d]	$IPrAuNTf_2$	-	**2a**	DCE	60	44

[a]The yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]1.0 equiv of **2a**, and 1.0 equiv of **3a** were used. [c]Isolated yields. [d]2 mol% of $IPrAuNTf_2$ was used, and the reaction was stirred for 20 h.

only 20% yield of **4a** (entry 3). $AuBr_3$ was significantly less efficient (entry 4). Among the screened gold catalysts, the N-heterocyclic carbene gold(I) complex showed higher activity, and 77% of **4a** could be achieved using $IPrAuNTf_2$ as the catalyst (entry 5). When the reaction was carried out with 5 mol % of IPrAuCl and 10 mol % of $AgNTf_2$, the yield of **4a** decreased to 58% (entry 6). Activation of IPrAuCl by other silver salts such as OTs or BF_4 was less effective (entries 7 and 8). To our delight, 82% of **4a** was obtained through decreasing the reaction temperature to 60 °C (entry 10). Other *N*-oxides showed lower reactivity (entries 11–13). The solvent screening (MeCN, toluene, and THF) indicated that toluene was also suitable for this reaction (entries 14–16). In the absence of a gold catalyst, no desired product was formed (entry 17). The use of $AgNTf_2$ also failed to give the desired product (entry 18).

With the optimized reaction conditions in hand, we next examined the substrate scope. A broad range of diynones with different R^1 or R^2 groups were compatible for this reaction. First, we checked the effects of the R^1 group at the alkyne terminus on this reaction. For aryl alkynes, whenever it bears electron-donating groups (*p*-^{t}Bu, *p*-OMe) or electron-withdrawing groups (*p*-F, *p*-Br, and *p*-CO_2Me), all worked very well to afford **4b**–**4f** in 67–81% yields (Scheme 3). Notably, sterically encumbered *o*-Me-aryl alkyne transformed into product **4g** in excellent yield within 10 h. 2-Naphthyl-substituted diynone proceeded efficiently (**4h**). The reaction with thienyl-substituted diynone was also suitable (**4i**). Alkenyl-substituted substrate afforded **4j** in moderate yield. A

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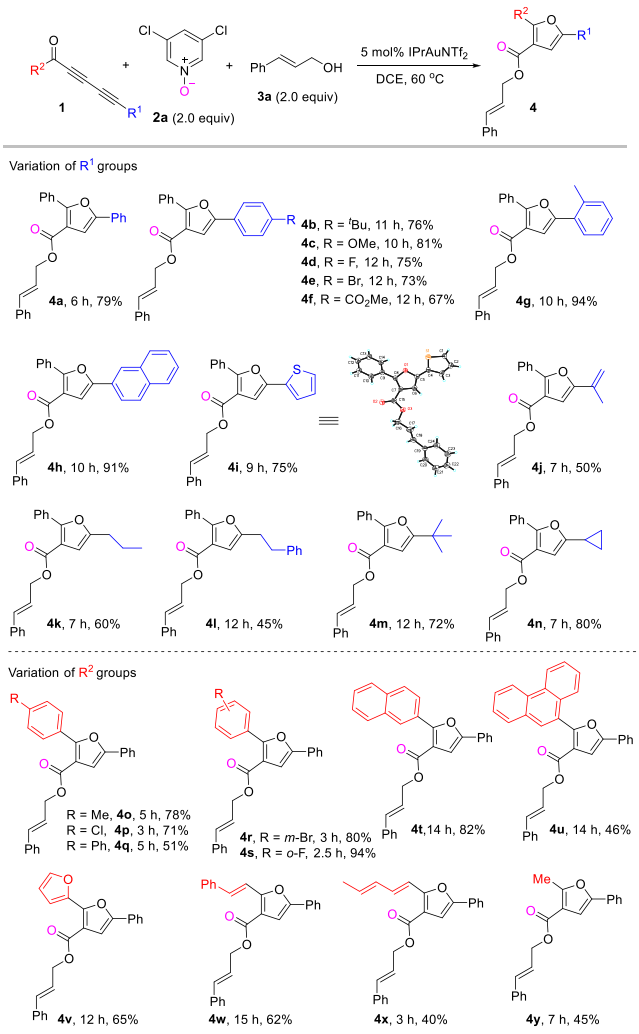
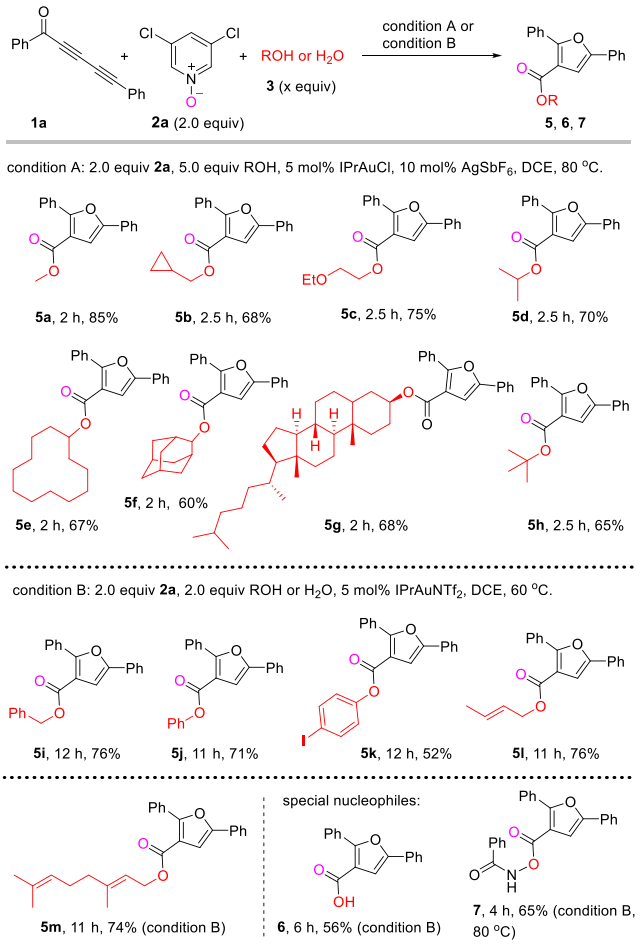
Scheme 3. Substrate Scope of Diynones



Scheme 4. Substrate Scope of Alcohols



variety of alkyl-substituted diynones cyclized smoothly. For example, normal alkyl, phenylethyl, *tert*-butyl, and cyclopropyl groups were all compatible to give **4k**–**4n** in 45–80% yields. Next, we examined the effects of the R^2 group on the keto moiety. The electronic properties of the R^2 group were explored. Aryl ketones with *p*-Me, *p*-Cl, *p*-Ph, *m*-Br, and *o*-F groups on the aryl rings all could be used as effective substrates for this reaction (**4o**–**4s**). It is noted that when *m*-Br- or *o*-F-substituted ketones were used as the substrates higher yields of **4r**–**4s** (80–94%) were obtained, possibly due to the enhanced reactivity of diynones by these electron-withdrawing groups. 2-Naphthyl-substituted ketone reacted smoothly (**4t**). However, with a 9-phenanthrenyl substituent, the desired **4u** was formed in only 46% yield. This is possibly due to the steric effect of the 9-phenanthrenyl group, and the substrate bearing the 2-furanyl group led to 2,2′-difuran **4v** in 65% yield. The reaction was also applicable to alkenyl- or dienyl-substituted substrates, which provided **4w**–**4x** in 62% and 40% yields, respectively. The alkyl ketone could also be used, leading to **4y** in 45% yield. The structure of **4i** was confirmed by X-ray crystallographic analysis.

We next turned our attention to explore the scope of alcohols using **1a** as the reaction partner (Scheme 4). We found that in the case of common alcohols the use of 5 mol % of IPrAuCl and 10 mol % of $AgSbF_6$ as the catalyst in the presence of 5 equiv of alcohols afforded the best results. Under these reaction conditions, a large variety of alcohols could be used as effective nucleophiles for this reaction. For example, primary alcohols such as methanol, cyclopropylmethanol, or 2-ethoxyethan-1-ol reacted with **1a** smoothly to afford **5a**–**5c** in good to high yields. Secondary alcohols were found to also be perfect substrates. For example, isopropanol, cyclododecanol, and 2-adamantanol transformed to **5d**–**5f** successfully. In addition, a natural product of cholesterol was proved to be a suitable substrate (**5g**). The reaction proceeded well with tertiary alcohol such as 2-methylpropan-2-ol (**5h**). Benzyl alcohol delivered the desired product **5i** in 76% yield. The use of phenol or 4-iodophenol as a nucleophile delivered **5j**–**5k** in 52–71% yield. Alkyl allylic alcohols such as crotonyl alcohol and geraniol could be efficiently incorporated into the products (**5l**–**5m**). In addition, water could also be used as the nucleophile, and 2,5-diphenylfuran-3-carboxylic acid **6** was formed in 56% yield. Phenylhydroxamic acid reacted smoothly with **1a** to give **7** in 65% yield. These results demonstrate the synthetic utility of this methodology.

To understand the reaction mechanism, various control experiments were carried out. It was known that ynones could undergo 1,3-oxygen transposition under gold catalysis.[12] Treatment of **1c** or **1l** with 5 mol % of $IPrAuNTf_2$ resulted in no formation of the transposed products via mono or double 1,3-oxygen transposition. Thus, it is likely that 1,3-oxygen transposition is not involved in our reaction (Scheme 5, eq 1). To learn if the α,α'-dioxo gold carbene intermediate is

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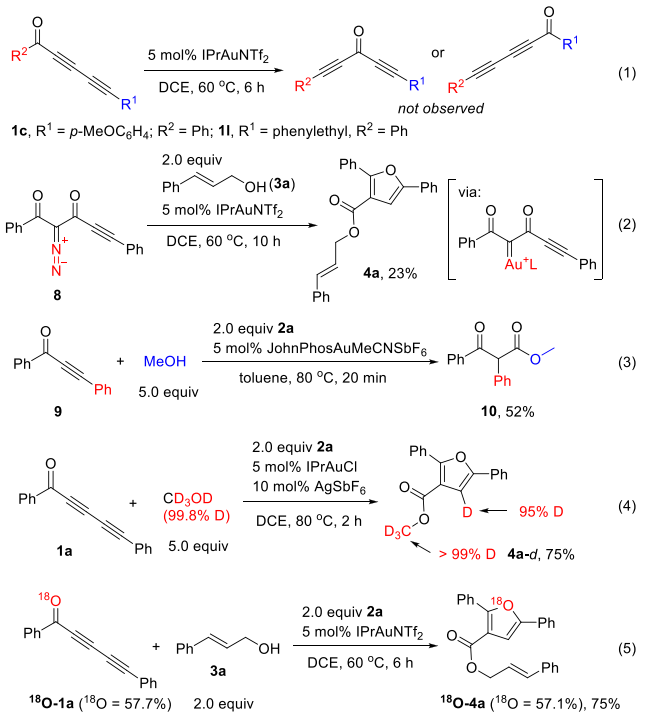
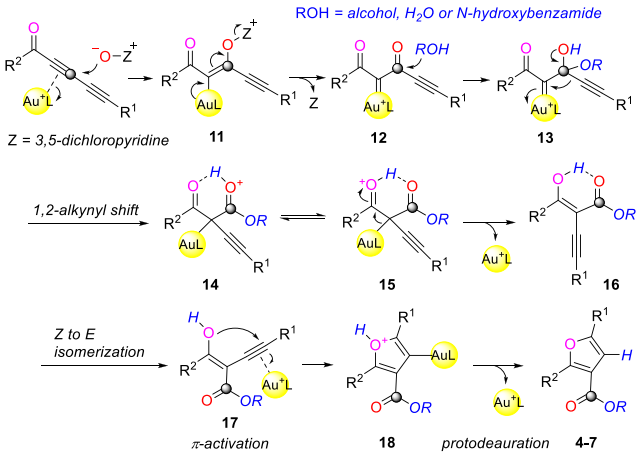
Scheme 5. Control Experiments



involved or not in this reaction, we synthesized 2-diazo-1,3-dione **8**. The reaction of **8** with allylic alcohol **3a** under the standard conditions afforded the same product **4a** in 23% yield, indicating that possibly the reaction proceeds via an α,α'-dioxo gold carbene (Scheme 5, eq 2). When ynone **9** was used instead of diynone **1a**, the product **10** was formed via nucleophilic attack of MeOH to gold carbene followed by 1,2-aryl migration (Scheme 5, eq 3). The results suggest that in the reactions of diynones with alcohols a 1,2-alkynyl migration might also be involved. To understand the deauration process, the cyclization of **1a** with 5.0 equiv of CD_3OD was performed. Furan **4a**-*d* with significant deuterium incorporation at the C-4 position was observed (Scheme 5, eq 4). These results strongly support the formation of a C-4-aurated furan intermediate. An ^{18}O-labeling experiment with ^{18}O-labeled substrate ^{18}O-**1a** was also performed. It converted to the corresponding furan ^{18}O-**4a** in 75% yield, in which the ^{18}O label is located at oxygen of the furan ring, indicating that this oxygen atom comes from the diynone (Scheme 5, eq 5).

Based on the above results, a plausible reaction mechanism is given in Scheme 6. Initially, alkyne activation by gold occurs to afford a π-alkyne gold complex, which is attacked by *N*-oxide regioselectively to give an alkenyl gold intermediate **11**. **11** fragmentizes into the α,α'-dioxo gold carbene species **12** via N−O bond cleavage. Subsequent nucleophilic attack of the alcohol to the highly electrophilic carbonyl group adjacent to the alkyne moiety generates intermediate **13**. This is followed by 1,2-alkynyl migration (pinacol type) to give intermediate **14**, which might be in equilibrium with **15** due to the proton shuttle between two carbonyls. Deauration of **15** affords enol intermediate **16**. Then *Z*/*E* isomerization followed by nucleophilic attack of the oxygen to alkyne and protodeauration lead to the furan products and regenerates the gold catalyst.

Scheme 6. Plausible Reaction Mechanism



In summary, we have developed a new and multicomponent strategy for the synthesis of functionalized furan-3-carboxylates based on gold-catalyzed oxidative cyclization of diynones with alcohols or water. Mechanistic studies revealed that a rare nucleophilic attack to the carbonyl group of the α,α'-dioxo gold carbene and 1,2-alkynyl group migration were involved as the key steps for this transformation. This method offers several advantages such as mild reaction conditions, high regioselectivity, wide functional group compatibility, and easily accessible starting materials. Further applications of this chemistry with a wide range of nucleophiles are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02389.

Experimental details and spectroscopic characterization of all new compounds, (PDF)

Accession Codes

CCDC 2091384−2091385 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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