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Letter

Nickel-Catalyzed Cyanation of Unactivated Alkyl Sulfonates with Zn(CN)$_2$

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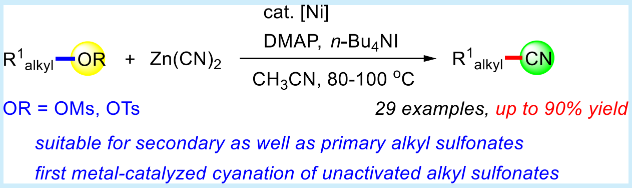
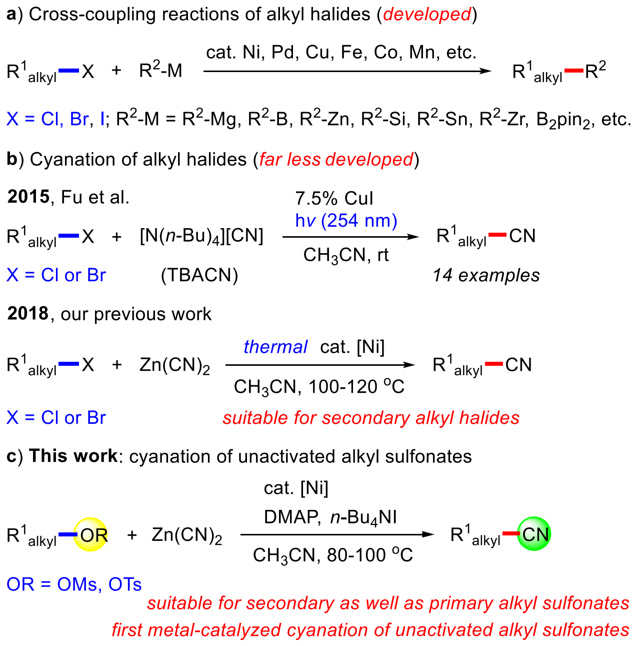
ABSTRACT: Cyanation of unactivated primary and secondary alkyl mesylates with Zn(CN)$_2$ catalyzed by nickel has been developed. The reaction provides an efficient route for the synthesis of alkyl nitriles with wide substrate scope, good functional group tolerance, and compatibility with heterocyclic compounds. Mechanistic studies indicate that alkyl iodide generated in situ serves as the reactive intermediate and the gradual release of alkyl iodide is crucial for the success of the reaction.



Transition-metal-catalyzed cross-coupling reactions have attracted great attention owing to their high selectivity and efficiency in the construction of carbon−carbon and carbon−heteroatom bonds under environmentally friendly conditions.[1] Usually, aryl electrophiles such as aryl halides and phenol derivatives, including sulfonates, phosphates, ethers, carbamates, carbonates, etc., have been employed as the electrophiles. Compared with aryl electrophiles, the coupling reactions of alkyl electrophiles are generally more challenging due to the low tendency of oxidative addition and the facile β-hydride elimination from alkylmetal intermediates.[2] In recent years, great progress has been achieved in metal-catalyzed cross-coupling reactions with alkyl halides. For example, alkyl halides have been found to couple well with Grignard reagents,[3a,b] organoboranes,[3c,d] organozinc,[3e,f] organosilicon,[3g3h] organotin,[3i,j] organozirconium reagents,[3k] B$_2$pin$_2$,[3l,m] etc. under transition metal catalysis (Scheme 1a).[3]

Scheme 1. Transition-Metal Catalyzed Coupling Reactions of Unactivated Alkyl Electrophiles



On the other hand, nitriles are versatile and efficient building blocks in organic chemistry as well as in medicinal chemistry.[4] Transition-metal-catalyzed cyanation of alkyl electrophiles would be one of the most promising methods for the synthesis of alkyl nitriles. However, such reports are quite limited. To the best of our knowledge, there are only two examples involving the metal-catalyzed cyanation of unactivated alkyl electrophiles.[5,6,7a] Fu and coworkers developed a copper-catalyzed and photoinduced cyanation of unactivated alkyl halides using TBACN (tetrabutylammonium cyanide) as the cyanide source (Scheme 1b).[6] Recently, we found that nickel could catalyze the cyanation[7] of unactivated secondary alkyl halides with Zn(CN)$_2$ in the presence of DMAP and n-Bu$_4$NCl under thermal conditions (Scheme 1b).[7a] Reactions of primary alkyl chlorides or bromides with Zn(CN)$_2$ were found to occur at generally high temperature (140 °C) without the need for nickel catalyst.[7a] Although these reactions are effective, methods for the preparation of alkyl halides are not always satisfactory. Alkyl halides are usually prepared through halogenation of the corresponding alcohols; however, in some cases, it suffers from low yields of the products and difficulty in separating the desired products from the

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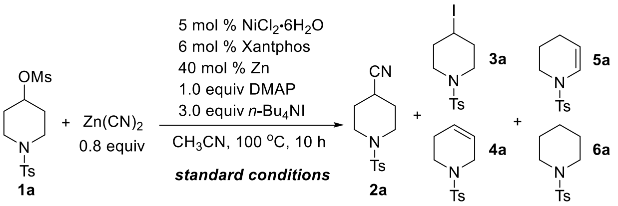
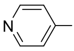
byproducts.[8] In this context, alkyl sulfonates are more attractive than alkyl halides for cross-coupling reactions because these compounds can be readily prepared from the easily available alcohols in generally high yields. Inspired by our previous work, we expected that alkyl sulfonates might also serve as efficient electrophiles for cyanation reactions. It was noted that alkyl sulfonates have rarely been used in nickel-catalyzed cross-coupling reactions,[9] possibly due to their low tendency to engage in a SET process that usually operate with alkyl halides. In this paper, we report the first example of nickel-catalyzed cyanation of alkyl sulfonates using $Zn(CN)_2$ as the cyanide source owing to its relatively lower toxicity (intraperitoneal, LD_{50} = 100 mg kg^{-1},[10a] compared with NaCN, KCN,[10b] intraperitoneal, LD_{50} = 4.72−5.55 mg kg^{-1})[10] and low solubility in organic solvents which was beneficial to mitigate catalyst poisoning by cyanide ions (Scheme 1c). The method also avoids the use of highly toxic reagents such as MCN (M = Na, K) as the cyanide source.[11] Although these reagents could be used for cyanation of alkyl sulfonates, the systematic studies on these reactions are quite rare. In some cases, the reactions suffer from an excess of cyanide,[11a,b] serious side reactions,[11c] and low yields.[11d,e]

Table 1. Optimization of the Reaction Conditions



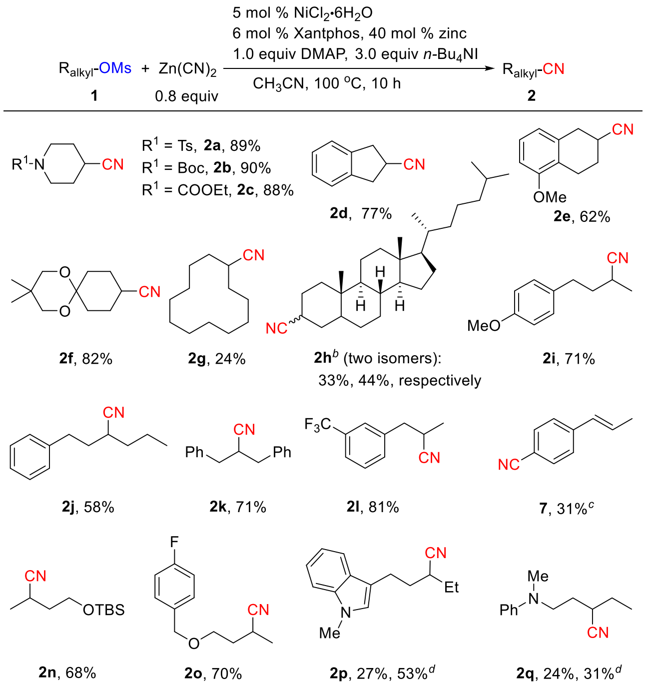
entry	deviation from the standard conditions	conversion of **1a** (%)	yield (%)[a] **2a**	**3a**	**4a**	**5a**	**6a**
1	none	97	88, 89[b]	-	-	2	4
2	no n-Bu_4NI	7	-	-	-	-	-
3	n-Bu_4NBr instead of n-Bu_4NI	100	18	-[c]	18	-	34
4	n-Bu_4NCl instead of n-Bu_4NI	100	-	-[d]	13	-	-
5	KI instead of n-Bu_4NI	57	41	-	2	2	-
6	2.0 equiv n-Bu_4NI was used	86	72	-	2	2	7
7	no DMAP	94	67	-	-	8	16
8	 NH_2 instead of DMAP	96	82	-	-	3	8
9	Cs_2CO_3 instead of DMAP	100	85	-	-	6	6
10	$NiCl_2(DME)$ instead of $NiCl_2·6H_2O$	100	72	-	5	-	17
11	$NiCl_2$ instead of $NiCl_2·6H_2O$	97	60	-	5	-	31
12	dppf instead of Xantphos	95	74	-	-	7	12
13	PCy_3 instead of Xantphos	94	-	21	35	-	34
14	2,2'-bpy instead of Xantphos	92	-	22	31	-	33
15	Mn instead of Zn	96	-	21	66	-	-
16	80 °C	48	36	-	-	-	12
17	no $NiCl_2·6H_2O$	94	-	18	39	-	33
18	no Xantphos	88	-	28	35	-	25
19	no Zn	94	-	28	61	-	-
20	OTs instead of OMs in **1a**	100	72	-	-	7	4
21	OAc or OBz instead of OMs in **1a**	6	-	-	-	-	-

[a]Determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield. [c]4-Bromo-1-tosylpiperidine was formed in 28% yield. [d]4-Chloro-1-tosylpiperidine was formed in 84% yield.

Our investigation commenced with the nickel-catalyzed cyanation of 1-tosylpiperidin-4-yl methanesulfonate **1a** as the model substrate. Initially, the reactions were examined under the conditions for cyanation of alkyl chlorides or bromides ($NiCl_2·6H_2O$/Xantphos/Zn/DMAP/n-Bu_4NCl or $Ni(acac)_2$/Xantphos/DMAP/Zn) reported in our previous paper.[7a] However, trace or no desired cyanation products were observed. The effects of nickel catalysts, ligands, reductants, additives, solvents, substrate concentration, etc. on the reaction were then studied, and the detailed results are shown in the Supporting Information. Finally, we were pleased to find that the desired reaction took place smoothly to give the alkyl nitrile **2a** in 88% yield at 100 °C using $NiCl_2·6H_2O$/Xantphos as the catalyst system in the presence of 40 mol % zinc powder (Adamas, 325 mesh), 1.0 equiv DMAP, and 3.0 equiv n-Bu_4NI (Table 1, entry 1). Zinc acts as a reductant to reduce Ni(II). It was found that the additive of n-Bu_4NI played a key role in this reaction because, without n-Bu_4NI, no desired product was observed (entry 2). The use of n-Bu_4NBr as the additive afforded **2a** in low yield, along with the formation of 4-bromo-1-tosylpiperidine, alkene **4a**, and dehalogenated product **6a** as the byproducts (entry 3). The results indicated that alkyl bromide might act as the active intermediate under this condition. When n-Bu_4NCl was added, the corresponding alkyl chloride was formed in 84% yield (entry 4). No product was found in this case, possibly due to the lower reactivity of the alkyl chloride toward cyanation compared with alkyl bromide. Based on these results, we assumed that alkyl iodide might be produced in the presence of n-Bu_4NI,[9d,12] which should be more reactive than alkyl bromides or alkyl chlorides. n-Bu_4NI might also act as a phase transfer reagent to promote the cyanide ion entering into the organic phase. When KI was employed instead of n-Bu_4NI, the yield of **2a** decreased to 41% (entry 5). Reducing the amount of n-Bu_4NI to 2.0 equiv caused an erosion in yield (entry 6). Without DMAP, **2a** was formed in 67% yield, along with the formation of alkene **5a** and dehalogenated product **6a**, indicating that DMAP could effectively reduce the side reactions (entry 7 vs entry 1). DMAP may also promote cyanide ion dissociation through the formation of a DMAP-$Zn(CN)_2$ complex and acts as a coligand as well.[7b] The use of 4-aminopyridine or Cs_2CO_3 instead of DMAP afforded **2a** in similar yields (82−85%, entries 8−9). $NiCl_2(DME)$ or $NiCl_2$ could also catalyze this reaction, albeit with lower yields of 60−72% (entries 10 and 11). Other bidentate phosphine ligands such as dppf gave **2a** in 74% yield, while the use of PCy_3 or 2,2′-bpy was not effective (entries 12−14). Control experiments indicated that $NiCl_2·6H_2O$, Xantphos, and Zn were indispensable (entries 17−19). Alkyl tosylate was also compatible for this reaction, while no desired products were observed using alkyl acetate or benzoate as the substrates (entries 20 and 21).

We next studied the substrate scope of this new cyanation reaction under the best reaction conditions (Table 1, entry 1). The results are shown in Scheme 2. Boc- or CO_2Et-protected piperidin-4-yl methanesulfonates could be cyanated efficiently in 88−90% yields (**2b**−**2c**). Cyclic substrates bearing benzene-fused five- or six-membered rings coupled smoothly with $Zn(CN)_2$ (**2d**−**2e**). Substrate **1f** containing a ketal moiety could be successfully converted to **2f** in 82% yield. Cyanation of **1g** bearing a large-sized ring afforded **2g** in low yield (24%). When the optically pure alkyl sulfonate **1h** derived from the nature product was used as the substrate, a mixture of two diastereomers (**2h**) was produced. The results revealed that the radical species might be generated during the reaction. Next, the reactivity of acyclic alkyl mesylates was investigated.

Scheme 2. Nickel Catalyzed Cyanation of Secondary Alkyl Mesylates[a]

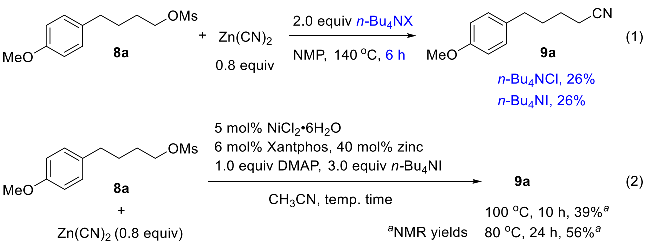


[a]Isolated yields. [Substrate] = 0.2 M. [b]β-Cholestanol methanesulfonate was used as the substrate. [c]1-(4-Bromophenyl)propan-2-yl methanesulfonate was used. [d]80 °C, 24 h.

Linear alkyl mesylates bearing aryl rings were well-suited for this reaction (**2i**−**2l**). The functionalities on the aryl rings such as −OMe or −CF$_3$ were tolerated. Mesylate **1m** (1-(4-bromophenyl)propan-2-yl methanesulfonate) containing an aryl bromide moiety converted to alkene **7** in 31% yield, indicating that dehydromesylation and cyanation of the C(sp^2)−Br bond occurred in this case. Alkyl ethers with an OTBS or a benzyl group also worked well, affording **2n**−**2o** in 68−70% yields. Under the standard conditions, substrate **1p** bearing an indole substituent afforded **2p** in only 27% yield. By lowering the reaction temperature to 80 °C, the yield of **2p** could be improved to 53%. Substrate **1q** with an amino group afforded **2q** in 31% yield at 80 °C.

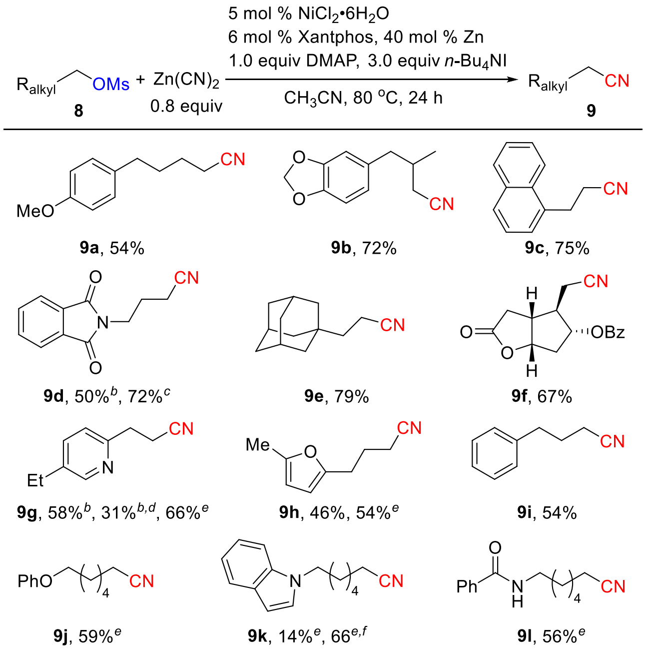
Encouraged by the above results, we next examined the reactivity of primary alkyl mesylates. We have found that primary alkyl halides could be cyanated directly without the need for nickel catalyst.[7a] However, when **8a** was subjected to our previous reaction conditions,[7a] only 26% of **9a** was obtained (Scheme 3, eq 1, with n-Bu$_4$NCl). Changing the n-Bu$_4$NCl to n-Bu$_4$NI could not improve the yield of the product. After treatment of mesylate **8a** with Zn(CN)$_2$ under the standard conditions for **2a**, the nitrile **9a** was formed in only 39% yield (Scheme 3, eq 2). Further optimization, including the change of the catalyst, ligands, and additives, could not improve the yield of **9a**,[13] possibly due to the low efficiency of the radical production from the primary alkyl iodide intermediates. To our delight, lowering the reaction temperature to 80 °C increased the yield of **9a** to 54%. Possibly, at the lower reaction temperature, the side reactions such as dehydroiodination could be reduced.

Scheme 3. Cyanation Reaction of 8a



Under the best reaction conditions for **9a**, the scope of various primary alkyl mesylates was examined (Scheme 4).

Scheme 4. Nickel Catalyzed Cyanation of Primary Alkyl Mesylates[a]

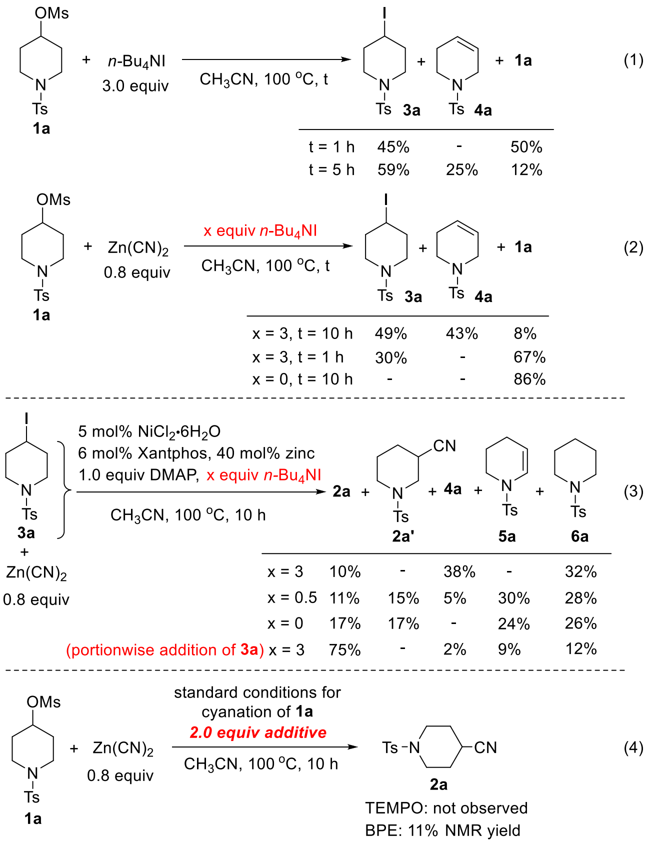


[a]Isolated yields. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]2.0 equiv of NaHCO$_3$ instead of DMAP was used. [d]100 °C, 19 h. [e]Ten mol % NiCl$_2$·6H$_2$O and 12 mol % Xantphos instead of 5 mol % NiCl$_2$·6H$_2$O and 6 mol % Xantphos were used. [f]60 °C, 26 h.

Substrates tethered with an aryl ring such as methylenedioxy-substituted phenyl or 1-naphthyl group transformed to **9b** and **9c** in higher yields of 72−75%. In the case of **9d** with an amide functionality, better yield was obtained (72%) using 2.0 equiv NaHCO$_3$ instead of DMAP. Adamantine-bearing alkyl mesylate gave the desired **9e** in 79% yield. **8f** derived from (−)-Corey lactone benzoate containing an ester substituent afforded **9f** in 67% yield, while the -OBz group remained unchanged. When substrate **8g** with a pyridyl ring was employed, the nitrile **9g** was formed in 58% yield. Raising the temperature from 80 to 100 °C did not improve the product yield. To our delight, through increasing the amounts of catalyst and ligand, **9g** could be formed in 66% yield. A furanyl-substituted alkyl mesylate was also cyanated smoothly (**9h**). Substrates tethered with various functional groups such as -OPh, -indolyl, and amide groups also worked well (**9j**−**9l**).

To gain insight into the reaction mechanism, various control experiments were carried out (Scheme 5).[13] The reaction of **1a** with n-Bu$_4$NI afforded 59% of alkyl iodide **3a** and 25% of alkene **4a** after 5 h (Scheme 5, eq 1). In the presence of

Scheme 5. Mechanistic Studies



t = 1 h	45%	-	50%
t = 5 h	59%	25%	12%

x = 3, t = 10 h	49%	43%	8%
x = 3, t = 1 h	30%	-	67%
x = 0, t = 10 h	-	-	86%

x = 3	10%	-	38%	-	32%
x = 0.5	11%	15%	5%	30%	28%
x = 0	17%	17%	-	24%	26%
(portionwise addition of 3a) x = 3	75%	-	2%	9%	12%

TEMPO: not observed
BPE: 11% NMR yield

$Zn(CN)_2$, **3a** was observed in 49% yield after 10 h, along with 43% of **4a**, while cyanation product **2a** was not formed (Scheme 5, eq 2). **4a** was not observed without *n*-Bu$_4$NI, indicating that **4a** should be formed during the iodination process. The results implied that alkyl iodide might be the active intermediate of the cyanation reaction. However, the nickel-catalyzed reaction of alkyl iodide **3a** with $Zn(CN)_2$ under the standard conditions gave **2a** only in low yield, along with the formation of **4a** and **6a** (Scheme 5, eq 3). We initially speculated that the excessive iodide ions in the reaction mixture might deactivate the nickel catalyst, thus lowering the reaction efficiency. To verify this point, the effect of the amount of *n*-Bu$_4$NI was investigated. Similar yield was observed by reducing the amount of *n*-Bu$_4$NI to 0.5 equiv, while the yield was slightly improved without *n*-Bu$_4$NI (**2a**, 17%), and in both cases, cyanation product **2a′** could also be observed. **2a′** might be formed via hydrocyanation of **4a**. A large amount of side products were observed in the above reactions. These results indicated that in the presence of stoichiometric amount of alkyl iodide, the side reactions such as dehydroiodination or hydrodeiodination reactions were significant increased. Interestingly, when the iodide **3a** was added in four portions to the reaction mixture, the yield of **2a** could be improved to 75%. Thus, it was concluded that the low concentration of the alkyl iodide is crucial for the success of the cyanation reactions due to the reduced side reactions. To maintain the low concentration of the alkyl iodide, it is possible that alkyl iodide participates the cyanation rapidly once it was generated. In fact, the alkyl iodide was not detected after stirring the mixture at 100 °C for 1 h under the standard reaction conditions for **2a**. Addition of a radical scavenger TEMPO (2,2,6,6-tetramethylpiperidinooxy) or BPE (1,1-diphenylethylene) inhibited the reaction, suggesting that a radical process might be involved (Scheme 5, eq 4). The above investigation suggests that the present reaction may proceed through the first formation of an alkyl iodide followed by nickel-catalyzed cyanation reaction through the Ni(I)/Ni(III) catalytic cycle proposed in our previous work.[7a]

In summary, we developed a facile approach for the synthesis of alkyl nitriles via nickel-catalyzed cyanation of unactivated alkyl sulfonates. Given the importance of the nitrile compounds in chemistry and biology, the method might find wide utility in pharmaceutical preparations and drug development. Mechanistic studies indicate that the in situ-generated alkyl iodide serves as the reactive intermediate, and the gradual release of alkyl iodide plays an important role for the success of the reaction. Further investigations on the detailed reaction mechanism and application of this chemistry 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.0c02722.

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

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Notes

The authors declare no competing financial interest.

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