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Base-Mediated Anti-Markovnikov Hydroamidation of Vinyl Arenes with Arylamides

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Cite This: *Org. Lett.* 2021, 23, 565−570 Read Online

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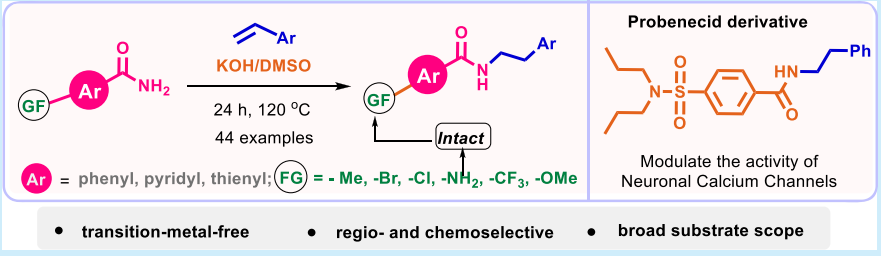

ABSTRACT: We investigated a base-promoted protocol for the intermolecular anti-Markovnikov hydroamidation of vinyl arenes with arylamides to furnish the arylethylbenzamides with excellent chemo- and regioselectivity. The reaction tolerates an extensive variety of functional groups and has been successfully extended with electronically varied handles, aminobenzamides, electron-rich/electron-deficient heterocyclic amides, and vinyl arenes to afford the hydroamidated products. Excellent chemoselectivity was observed for the amide group over amine. The proposed mechanism and vital role of the solvent was well supported by deuterium labeling studies and control experiments.

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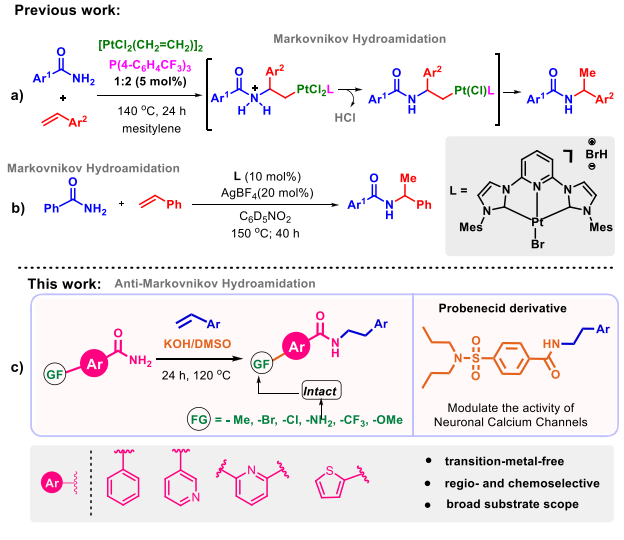
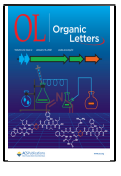
The amide pharmacophore is ubiquitous in diverse pharmaceutical and biologically active molecules.[1a,b] Recently, the amide linkages have shown a potent activity against COVID-19 respiratory syndrome.[1c−e] Amides are the common templates for amino acids, which are considered as building blocks of peptides and proteins.[2] The construction of suitably functionalized amide frameworks is useful in many industrial and natural product syntheses.[3] In the past few decades, many traditional approaches for transition-metal-catalyzed hydroamination of *N*-heterocycles and primary/secondary amines with alkynes and alkenes have been well explored.[4−6] Base-mediated nucleophilic addition of heterocycles as well as amine moieties has also been known from many renowned reactions reported in the literature.[7,8] However, due to the formation of highly stable resonating structures and poor nucleophilicity hydroamination of amides is still challenging.[9−11]

An elegant approach to Markovnikov's addition[12a,b] of amides on to vinyl arenes using Pt complex was depicted by Widenhoefer and co-workers[12c] in 2005 (Scheme 1a). A similar type of chemistry has been demonstrated by the Limbach[13] group using cationic platinum(II) complexes with bi- or tridentate NHC ligands for the hydroamidation of unactivated alkenes (Scheme 1b). Asymmetric hydroamination permits the straightforward and selective formation of a new C−N bond as a convenient methodology toward valuable synthons.[14a,b] In 2012, Hartwig et al. described the addition of 4-*tert*-butylbenzamide to 1-octene in the presence of iridium catalyst.[14c] In recent years, transition-metal-free reactions have

Scheme 1. Strategies for the Hydroamidation of Vinyl Arenes



Received: December 10, 2020
Published: January 4, 2021



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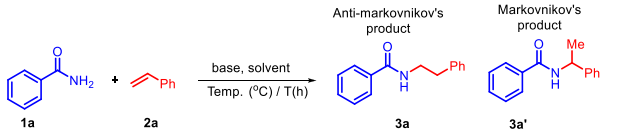
https://dx.doi.org/10.1021/acs.orglett.0c04084
Org. Lett. 2021, 23, 565−570

extended its relevance due to its low toxicity, cost-effectiveness, and no requirement for noncommercial ligands in chemical reactions.[15] In continuation of our ongoing research on base-promoted reactions[16] and hydroamination chemistry,[17] we anticipated that the direct hydroamidation of alkene could occur via KOH-DMSO assisted nucleophilic addition (Scheme 1c).

To explore the base-assisted nucleophilic addition we began with the examination of a several bases and solvent reported in the literature using benzamide **1a** and styrene **2a** as a model substrate (Table 1). Inspired by our previous conditions,[17] we

Table 1. Optimization Table[a]



entry	base	solvent	time (h)	temp (°C)	yield[b] (%) 3a
1[17]	KOH	DMSO	0.5	120	c
2	KOH	DMSO	6	120	30
3	KOH	DMSO	12	120	48
4	KOH	DMSO	24	120	80
5	KOH	DMSO	24	80	30
6[d]	KOH	DMSO	24	120	c
7	KOH	EtOH	24	70	trace
8	KOH	EG	24	120	55
9	KOH	NMP	24	120	61
10	KOH	THF	24	60	c
11	KOH	toluene	24	100	c
12	K_2CO_3	DMSO	24	120	40
13	K_3PO_4	DMSO	24	120	50
14	Et_3N	DMSO	24	120	c

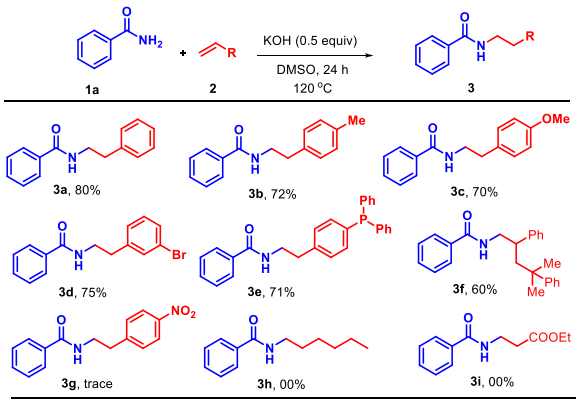
[a]Reactions were carried out using 0.5 mmol of **1a**, **2a** (0.8 mmol), and base (0.5 equiv) in 2.0 mL of solvent. [b]Isolated yield. [c]No reaction. [d]Base (0.2 equiv). **3a′** product was not obtained. EG = ethylene glycol, NMP = *N*-methylpyrrolidone, THF = tetrahydrofuran.

carried out the reaction of **1a** with alkene **2a** using KOH in DMSO at 120 °C for 0.5 h, but the conversion did not initiate (entry 1). The promotional effect of time elevates the yield of the product **3a** (entries 2−4). On lowering the reaction temperature, a 30% yield of the hydroamidated product was observed (entry 5). When 0.2 equiv of KOH was loaded in the system, the nucleophilic addition reaction did not occur (entry 6). Exchanging the solvents EtOH, ethylene glycol, NMP, THF, and toluene with KOH proved to be inferior for the reaction (entries 7−11). Different bases such as K_2CO_3, and K_3PO_4 were studied, and it was found that the nature of bases, as well as their counterions, influenced the reactivity of the hydroamidation reaction and provided compound **3a** in moderate yields (entries 12 and 13), while no product was observed with Et_3N (entry 14).

To understand the possible reason for the selective formation of anti-Markovnikov product, quantum chemical calculations were accomplished using the B3LYP/6-311+G(d) method. Complete optimization of the 3D structures of **1a**, **2a**, **3a**, and **3a′** (Table 1) were performed using the Berny optimization procedure. The enthalpy of the reactions was carried out by estimating the relative energies. The formation of **3a** (anti-Markovnikov product) is a thermodynamically favorable process because the energy difference between the reactants and product **3a** is negligible (0.028 kcal/mol); i.e., the reactant and product exist in equilibrium. Alternatively, the product **3a′** (Markovnikov's) formation is an endergonic process by 4.18 kcal/mol and hence is not a preferred path (as supported by experimental observation).

With the optimized reaction conditions in hand, we extended the scope of the developed protocol with various arylalkyl alkenes (Scheme 2). The reaction of benzamide **1a**

Scheme 2. Scope of Vinyl Arenes[a,b]



[a]Optimized conditions (entry 4, Table 1). [b]Isolated yield.

with styrene **2a**, electron-releasing alkenes **2b** (4-Me), and **2c** (4-OMe) furnished the products **3a−c** in 70−80% yields. Notably, the halogen-substituted styrene **2d** effectively gave the corresponding hydroamidated product **3d** in 75% yield. It is worth noting that reaction of **1a** with a bulky and sterically hindered alkene such as diphenyl(4-vinylphenyl)phosphine **2e** and (4-methylpent-1-ene-2,4-diyl) dibenzene **2f** provided the desired products **3e** and **3f** in 71 and 60% yield, respectively. However, the 4-nitrostyrene **2g**, aliphatic alkene **2h**, and acrylate **2i** were incapable of producing the hydroamidated product (Scheme 2).

Encouraged by the above results, the reaction of alkene **2** with electronically bias ring/substituents on the amide partner was performed (Scheme 3). The reaction of amide **1b** bearing an electron-releasing methyl group provided the desired hydroamidated products **4a−f** in 60−79% yields. The reaction of 4-methoxybenzamide **1c** with styrene **2a** was fruitful in providing the product **4g** in 78% yield. It was interesting to note that the 4-hydroxybenzamide **1d** selectively gave the hydroamidated product **4h** in 65% yield. However, strong electron-withdrawing nitro-substituted benzamide **1e** did not undergo the addition reaction smoothly. The addition of 3-(trifluoromethyl) benzamide **1f** on to alkene **2a** furnished the product **4j** in 81% yield. The halogen and electron-withdrawing group containing alkenes **2j** (4-Cl) and **2k** (4-CF_3) were successful in delivering the nucleophilic addition product **4k−l** in good yield. When benzamide **1g** containing a bromo substituent at the *ortho* position of aryl ring was used for the reaction, the desired addition products **4m−o** were obtained in 69−78% yields. In contrast to *o*-bromobenzamide, the para-substituent **1h** gave 4-bromo-*N*-phenethylbenzamide **4p** in 80% yield. A sluggish reaction of 4-fluoro-3-formylbenzamide **1i** with **2a** was observed (Scheme 3).

Subsequently, we explored the chemoselectivity of the reaction using aminobenzamides (Scheme 4). To study the chemoselective hydroamidation, we carried out reaction

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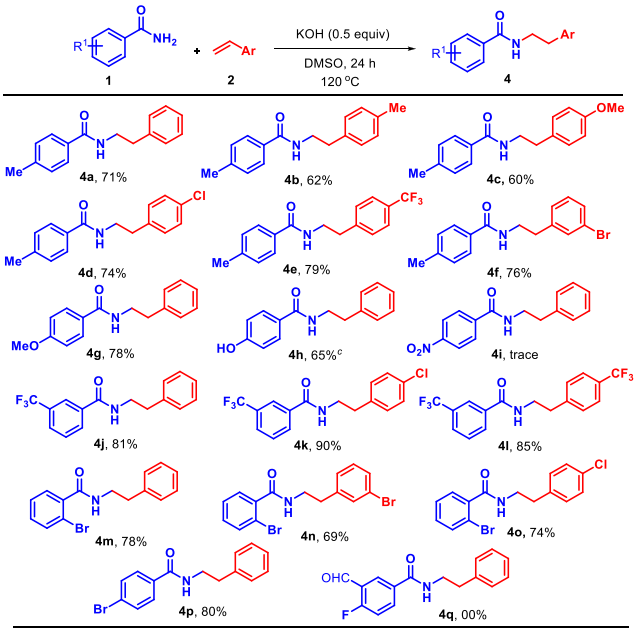
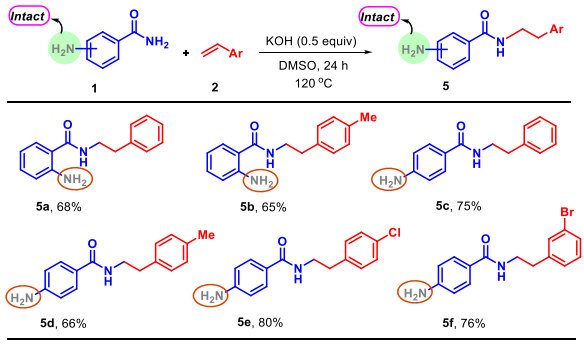
Scheme 3. Scope of Aryl Amides[a,b]



[a]Optimized conditions (Table 1, entry 4). [b]Isolated yield. [c]Using 2.0 equiv of KOH

Scheme 4. Scope of Chemoselective Hydroamidation[a,b]



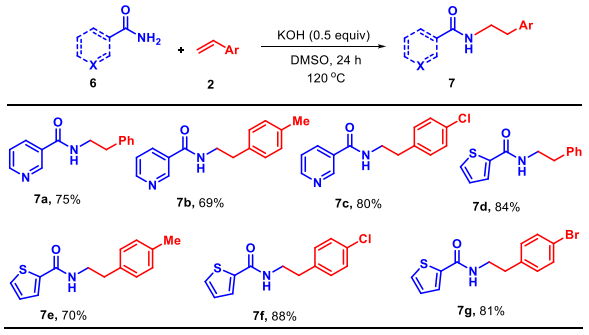
[a]Optimized conditions (Table 1, entry 4). [b]Isolated yield.

between 2-aminobenzamide (**1j**) and 4-aminobenzamide (**1k**) with vinyl arenes **2a**,**b**, **2j**, and **2d**; the hydroamidated products **5a**,**b**, and **5c**−**f** were obtained chemoselectively in 65−80% yields without effecting the 1° amino group (Scheme 4).

The scope of this base-assisted hydroamidation was further explored by using electron-deficient and electron-rich heterocyclic amides **6a** and **6b** (Scheme 5). Reaction of both the amides **6a** and **6b** with vinyl arenes **2a**,**b**, **2j**, and **2l** provided the respective hydroamidated products **7a**−**g** in 69−88% yields (Scheme 5).

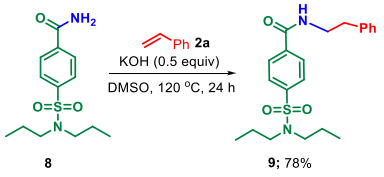
Probenecid has shown curative activity toward gout and hyperuricemia diseases. To our delight, the conversion of 4-(*N*,*N*-dipropylsulfamoyl)benzamide **8** produced the pharmaceutically promising 4-(*N*,*N*-dipropylsulfamoyl)-*N*-phenethyl benzamide **9** in 78% yield (Scheme 6). In order to observe the comparative hydroamidation studies between styrene (**2a**) and phenylethyne **10a** and **10b** with benzamide (**1a**), we carried out a control experiment (Scheme 7a) using 0.5 equiv of KOH at 120 °C. We observed that alkyne hydroamidated product **11a**,**b** was obtained in 77−72% yield within 15 min; however, the formation of product **3a** was not observed (Scheme 7a).[18]

Scheme 5. Scope of Heterocyclic Amides[a,b]

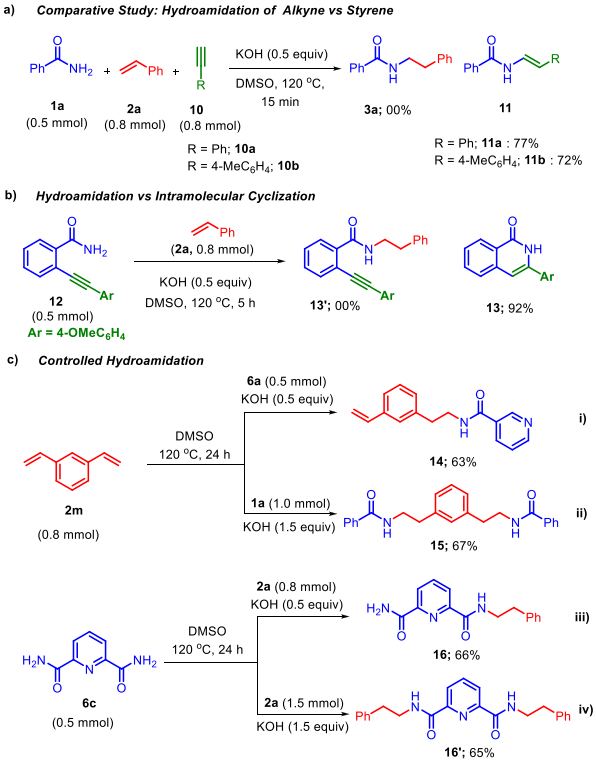


[a]Optimized conditions (entry 4, Table 1). [b]Isolated yield.

Scheme 6. Late-Stage Modification of Probenecid Derivative



Scheme 7. Comparative and Selectivity Hydroamidation Studies



In another set of control experiments, *o*-arylalkyne benzamide **12** was reacted with styrene (**2a**); an intramolecular cyclized isoquinoline **13** was obtained in 92% yield, and no hydroamidated product **13′** was observed (Scheme 7b).

Further, to study the selective hydroamidation of bis-amide **6c** and 1,3-divinylbenzene **2m** we performed four sets of control experiments (Scheme 7c, i−iv) and monitored the formation of products. In the first set of reactions, we reacted **2m** with **6a** (0.5 mmol) using 0.5 equiv of KOH at 120 °C for

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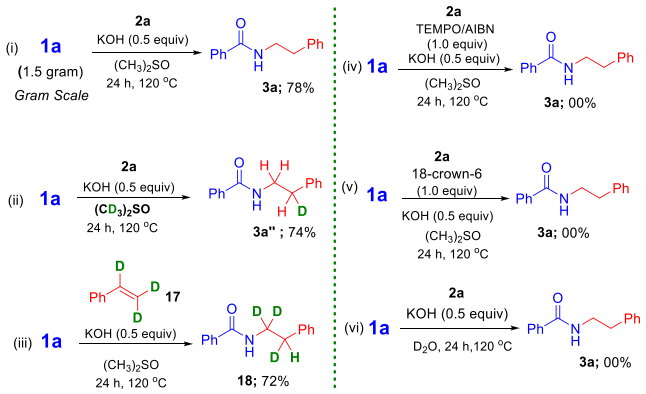
24 h; mono-hydroamidated product **14** was observed in 63% yield (Scheme 7c, i). However, the reaction of 1,3-divinylbenzene **2m** with benzamide (**1a**) using 1.5 equiv of KOH provided bis-hydroamidated product **15** in 67% yield (Scheme 7c, ii). Another control experiment was carried out between a bis-amide **6c** and styrene **2a**. It was observed that the use of 0.5 equiv of KOH provided the mono-hydroamidated product **16** in 66% yield; however, bis-hydroamidated product **16′** was obtained in 65% yield using 1.5 equiv of KOH (Scheme 7, iii, iv).

In addition, to support the proposed mechanistic pathway, assorted preliminary experiments were performed (Scheme 8).

Scheme 8. Mechanistic Control Experiments

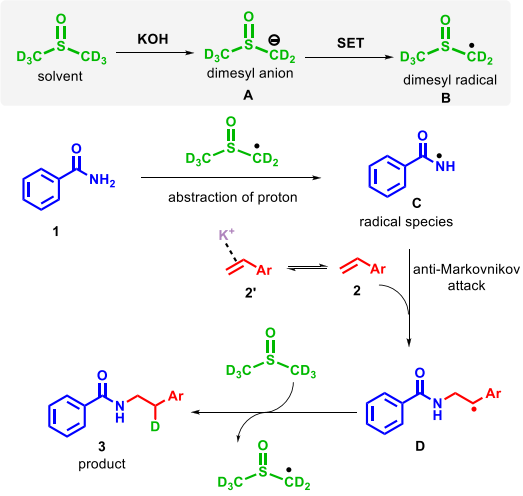


The reaction of **1a** with styrene **2a** was conducted under N_2 atmosphere, and the hydroamidation reaction occurred smoothly to provide product **3a** in good yield (see the Supporting Information). We performed gram-scale experiments for the hydroamidation reaction using benzamide **1a** and styrene **2a** as the starting substrate. The gram-scale reaction was successful in providing the desired product in 78% yield (eq i). Initially, we thought that the source of $-CH_2$ protons in the addition linkage between amide and alkene came from the DMSO solvent. In order to determine the source of protons, the reaction of benzamide **1a** with styrene **2a** was conducted in DMSO-d_6. The deuterated product **3a′′** was isolated in 74% yield with a single H−D exchange, indicating the proton comes from solvent the (eq ii).

For further validation, we planned the reaction of benzamide **1a** and deuterated styrene-d_3 **17** in KOH/DMSO; we fruitfully obtained the deuterated product **18** in 72% yield, confirming the anti-Markovnikov mechanism of hydroamidation (eq iii). We further examined the reaction of **1a** with **2a** in TEMPO/AIBN at 120 °C, where no formation of hydroamidated product **3a** infers that the reaction follows the radical pathway (eq iv). The hydroamidation reaction failed in the presence of 18-crown ether (1.0 equiv), which further validates the mechanism and deduces that the K^+ ion polarizes the alkene (eq v). Hydroamidated product was not observed when the reaction of benzamide **1a** with styrene **2a** was performed in the presence of heavy water. This illustrate that KOH/DMSO is essential for the protonation during nucleophilic addition linkage (Scheme 8, vi).

On the basis of the preceding mechanistic studies,[19,20] we put forth a reasonable mechanistic hypothesis as described in Scheme 9. The mechanism is initiated by the generation of dimesyl radical **B**[21] via a single electron transfer (SET) from dimesyl anion **A**. Then amide **1** is induced by a dimesyl radical

Scheme 9. Proposed Mechanism



B in the presence of base to form amidoyl radical species **C**.[22] The radical species **C** reacts with vinyl arene **2** in anti-Markovnikov fashion to form species **D** (a stable benzyl radical). After the abstraction of a deuterium atom from DMSO-d_6, monodeuterated product **3** is formed and the dimesyl radical is regenerated.

In conclusion, this study disclosed the first example of anti-Markovnikov addition of aryl amides on vinyl styrenes under metal-free conditions with excellent chemo- and regioselectivity. The generality of the reaction was manifested by the broad scope of electron-donating and electron-withdrawing aryl amides and vinyl arenes. The versatility of the reaction has been demonstrated by performing controlled mono- and bis-hydroamidation reactions of 1,3-divinylbenzene and pyridine-2,6-dicarboxamide. The methodology was further extended for the late-stage modification of pharmaceutically important probenecid. A proposed possible mechanism was established by the control experiments, isotopic labeling studies, and capturing of K^+ ion using 18-crown-6.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04084.

Data and spectral copies of ^1H, ^{13}C NMR, and HRMS for target compounds (PDF)

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https://dx.doi.org/10.1021/acs.orglett.0c04084
Org. Lett. 2021, 23, 565−570

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The work was supported by IoE/FRP/PCMS/2020/27 and USIC for instrumentation facilities. A.Y.U. and P.M. are thankful for the UGC for fellowships.

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https://dx.doi.org/10.1021/acs.orglett.0c04084
Org. Lett. 2021, 23, 565−570