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Letter

Nickel-Catalyzed β-Regioselective Amination/Cyclization of Ynamide-Nitriles with Amines: Synthesis of Functionalized 3-Aminoindoles and 4-Aminoisoquinolines

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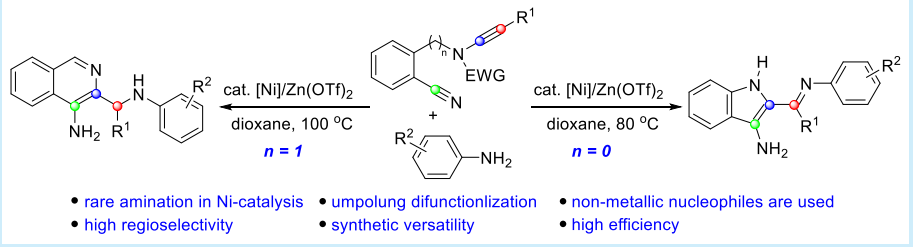

ABSTRACT: A highly regioselective nickel/Lewis acid catalyzed amination/cyclization of ynamide-nitriles with amines involving β-addition has been developed. The reaction offers an attractive and efficient route for the synthesis of 3-aminoindoles and 4-aminoisoquinoline derivatives. The Ts-group on the ynamide acts as a directing group to produce the alkenyl nickel species with high regioselectivity.

Ynamides have emerged as versatile and important building blocks in organic chemistry during the past two decades. They have been shown to engage in a wide range of transformations due to their high reactivity caused by the polarizing effect of the nitrogen on the alkyne, such as in transition-metal-catalyzed cyclizations, cycloadditions, carbometalation, ring-closing metathesis, rearrangements, radical reactions, etc.[1] Usually, α-addition to the triple bond in ynamides occurs due to the polarity of the ynamides (Scheme 1a), whereas the β-addition has much less been explored, especially in intermolecular processes.[2] In this context, most of the studies related to the intermolecular β-additions concentrated on the chelation controlled regioselective reactions (Scheme 1b). That is, the reaction is directed by chelation of the metal with the electron-withdrawing group, usually, an oxazolidinone group, to give a β-addition intermediate **I**, which can undergo further transformations to furnish the functionalized products. This includes carbocupration,[3] Rh-[4] or Cu[5]-catalyzed carbozincation, Rh-catalyzed arylation with arylboronic acids, arylboronates, and triarylboroxines,[6] Cu-catalyzed addition of Grignard reagents,[7] silyl-[7a,8] and boryl-metalation,[9] etc.[10] Although much progress has been achieved, stoichiometric amounts of organometallic reagents were usually required as the nucleophiles in these reactions, and some of them are air- and moisture-sensitive and suffer from low stability and low functional-group tolerance. Ideally, the use of nonmetallic reagents such as amines as the nucleophiles to initiate the β-additions would be of high interest since these nucleophiles are easily available and inexpensive. On the other hand, hydroamination of alkynes is a well-known process for the synthesis of imines, enamines, and heterocycles.[11] Early transition metals, rare earth metal complexes, and palladium and gold complexes are often used in hydroamination reactions. There are few examples using inexpensive late-transition-metals such as nickel as the catalyst in the hydroamination of alkynes, and the reported reactions usually require harsh reaction conditions and limited scope.[12] Only a few reports on metal-catalyzed intermolecular hydroamination[13] or amination/cyclizations[14] of ynamides with anilines are known, and most of the studies rely on gold-based systems via α-addition (e.g., Scheme 1c[13]). In this paper, we describe a nickel-catalyzed cyclization of ynamide-nitriles with primary anilines involving β-regioselective addition, which provides an efficient and attractive route for the synthesis of highly functionalized 3-aminoindoles and 4-aminoisoquinolines (Scheme 1d). To the best of our knowledge, this is the first example which involves nickel-catalyzed amination of ynamide derivatives.[15]

To test the feasibility, we initially investigated the nickel-catalyzed reaction of ynamide-nitrile **1a**[16] with 4-fluoroaniline (Table 1). After evaluation of the reaction parameters such as

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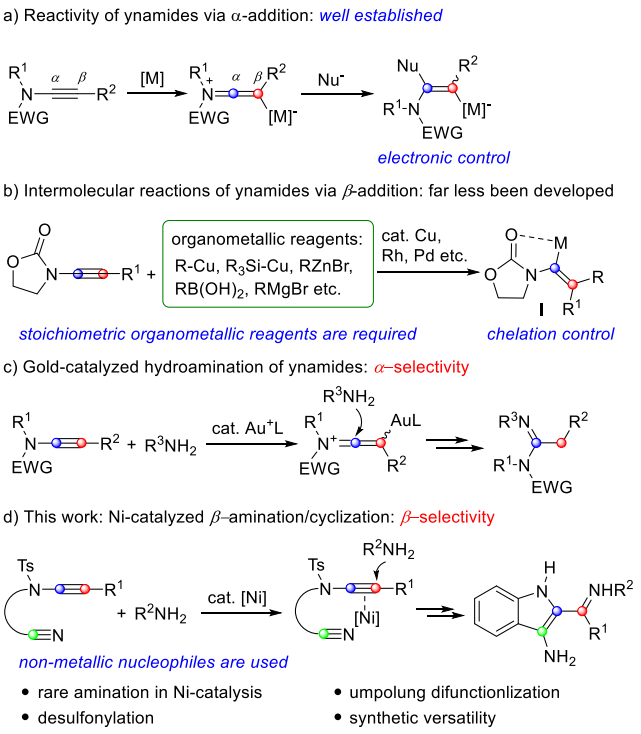
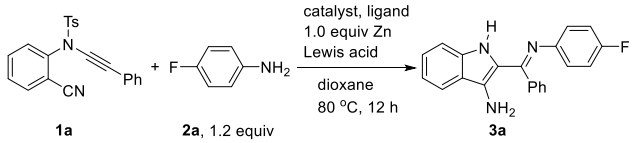
Scheme 1. Transition-Metal-Catalyzed Amination of Ynamides



nickel catalysts, ligands, additives and solvents (the detailed results are shown in the Supporting Information), we found that the addition of a Lewis acid played an important role for this reaction. For example, the 3-aminoindole **3a** was formed in 77% yield by the use of $NiCl_2$(DME) (10 mol %), dppp (10 mol %), Zn powder (1.0 equiv, alfa, 100 mesh) and $Zn(OTf)_2$ (20 mol %) in dioxane at 80 °C (Table 1, entry 1). Without $Zn(OTf)_2$, only 38% of **3a** was formed (entry 2). The structure of **3a** was confirmed by X-ray crystallographic analysis.[17] Interestingly, the results indicated that the Ts-group was eliminated during the reaction. Other ligands such as $PMePh_2$ or Xantphos are much less effective (entries 3−4). NiI_2 also showed high catalytic performance for this reaction (entry 5). A preassembled nickel phosphine complex $NiCl_2$(dppp) catalyzed the reaction also efficiently (entry 6). When $Sc(OTf)_3$ or $Al(OTf)_3$ were used instead of $Zn(OTf)_2$, **3a** could be formed in 48−63% yields, whereas low yield was observed with BPh_3 (entries 7−9). We suggested that Lewis acid might play a role by increasing the electrophilicity of the cyano group through coordination, thereby accelerates the nucleophilic addition process. Increasing the amount of $Zn(OTf)_2$ did not give a significant effect on the product yield (entry 10). The catalyst loading could be reduced to 5 mol %, resulting in a comparable yield of **3a** to that obtained using 10 mol % nickel catalyst (entry 11). The reaction also progressed smoothly in THF (entry 12). Decreasing the temperature to 50 °C or lowering the amount of Zn to 50 mol % reduced the yield of **3a** (entries 13−14). As expected, no products were formed without Ni catalyst, dppp, or Zn powder (entries 15−17). It was noted that when Zn powder derived from another chemical company (Admas, 325 mesh) was used, 1.0 equiv of Lewis acid was required to consume the starting material completely (entries 19−20). 3-Aminoindole derivatives are of high interest in pharmaceutical development, which

Table 1. Optimization Studies for the Formation of 3a



entry	catalyst	ligand (mol %)	Lewis acid (mol %)	yield (%)[a]
1	$NiCl_2$ (DME) (10)	dppp (10)	$Zn(OTf)_2$ (20)	77
2	$NiCl_2$ (DME) (10)	dppp (10)	–	38 (6)
3	$NiCl_2$ (DME) (10)	$PMePh_2$ (20)	$Zn(OTf)_2$ (20)	20 (7)
4	$NiCl_2$ (DME) (10)	Xantphos (10)	$Zn(OTf)_2$ (20)	– (72)
5	NiI_2 (10)	dppp (10)	$Zn(OTf)_2$ (20)	77
6	**$NiCl_2$(dppp) (10)**	–	**$Zn(OTf)_2$ (20)**	**78**
7	$NiCl_2$(dppp) (10)	–	$Sc(OTf)_3$ (20)	63 (3)
8	$NiCl_2$(dppp) (10)	–	$Al(OTf)_3$ (20)	48 (7)
9	$NiCl_2$(dppp) (10)	–	BPh_3 (20)	16 (11)
10	$NiCl_2$(dppp) (10)	–	$Zn(OTf)_2$ (100)	78
11	**$NiCl_2$(dppp) (5)**	–	**$Zn(OTf)_2$ (20)**	**81**
12	$NiCl_2$(dppp) (5)	–	$Zn(OTf)_2$ (20)	71[b]
13	$NiCl_2$(dppp) (5)	–	$Zn(OTf)_2$ (20)	68[c] (12)
14	$NiCl_2$(dppp) (5)	–	$Zn(OTf)_2$ (20)	35[d] (37)
15	–	dppp (5)	$Zn(OTf)_2$ (20)	– (70)
16	$NiCl_2$(DME) (5)	–	$Zn(OTf)_2$ (20)	– (81)
17	$NiCl_2$(dppp) (5)	–	$Zn(OTf)_2$ (20)	–[e] (61)
18	$NiCl_2$(dppp) (5)	–	–	25 (35)
19	$NiCl_2$(dppp) (10)	–	$Zn(OTf)_2$ (20)	31[f](25)
20	$NiCl_2$(dppp) (10)	–	$Zn(OTf)_2$ (100)	78[f]

[a]NMR yields using 1,3,5-trimethoxybenzene as an internal standard. The yields of the unreacted **1a** are shown in parentheses. [b]THF was used. [c]50 °C. [d]50 mol % Zn was used. [e]Without Zn powder. [f]1.0 equiv Zn (Adamas 325 mesh) was used.

exhibit a wide range of biological activities.[18] However, the synthetic route for 3-aminoindole is limited;[19] our method provides a straightforward route for these heterocycles.

With the optimized reaction conditions established, the substrate scope of this nickel-catalyzed cascade amination/cyclization was explored. The scope of the anilines was evaluated first using **1a** as the reaction partner (Scheme 2). During this process, we found that the 5 mol % catalyst loading was not effective in some cases, thus 10 mol % $NiCl_2$(dppp) was used in most of the cases (the conditions shown in Table 1, entry 6) to achieve the better results. A wide variety of anilines bearing either electron-donating or electron-withdrawing groups was suitable for this transformation. For example, anilines bearing an electron-deficient *o*-F, *p*-Cl, *p*-COPh, *p*-CO_2Et, or *p*-CN group were converted into the corresponding products **3b−f** in 35−54% yields. The use of electron-neutral aniline resulted in the formation of **3g** in 76% yield. Anilines with an electron-donating group such as *p*-Me, *p*-OMe, or *p*-^{t}Bu group gave higher yields of **3h−j** (76−81%) than those with electron-deficient groups, possibly due to the stronger nucleophilicity of these amines. Introduction of a *N*,*N*-dimethyl at the *para*-position of the aryl ring resulted in a lower yield of **3k** (28%), possibly due to the competitive coordination of this amino group with the nickel catalyst or a Lewis acid. The 3,5-dimethylaniline and 4-phenylaniline gave the corresponding product **3l** and **3m** in 40−45% yields. When the sterically bulkier 1-naphthylamine was employed, the

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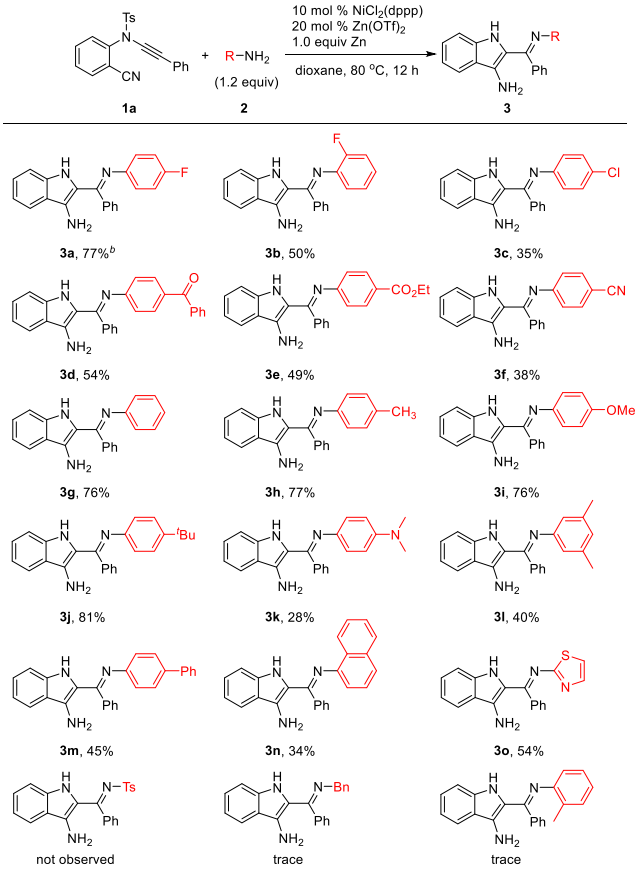
Scheme 2. Scope of Anilines[a]



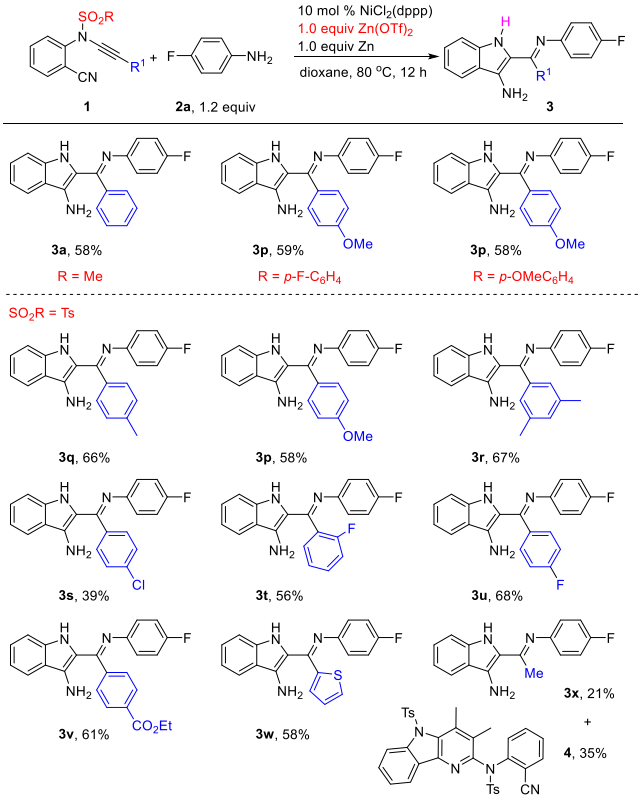
[a]Isolated yields. [b]5 mol % $NiCl_2$(dppp) was used.

corresponding product **3n** was formed in a lower yield (34%), indicating that the reaction is sensitive to the steric effects. In this case, most of the substrate **1a** was consumed, and the reaction was not clean. Heteroaryl amines such as 2-aminothiazole were also compatible (**3o**). However, no apparent product or trace product was observed with $TsNH_2$, benzyl amine, or *o*-methylaniline, respectively.

Next, the scope of ynamides was investigated by the reactions with 4-fluoroaniline (Scheme 3). The effect of the electron-withdrawing group of the ynamide was first examined. The *N*-Ms substrate afforded **3a** in 58% yield, which is lower than that obtained from the *N*-Ts-substituted one. *N*-*p*-Fluorobenzenesulfonyl or *N*-*p*-methoxybenzenesulfonyl-substituted ynamides were all suitable for this reaction, furnishing **3p** in 58−59% yields. Substrates with an electron-donating group such as *p*-Me, *p*-OMe, or 3,5-dimethyl on the terminal aryl ring underwent the cyclization reactions smoothly, furnishing **3q**, **3p**, and **3r** in 58−67% yields. Ynamides with a variety of electron-withdrawing groups such as *p*-Cl, *o*-F, *p*-F, or *p*-CO_2Et on the aryl ring reacted smoothly with **2a**, furnishing **3s**−**3v** in 39−68% yields. Notably, a chlorine substituent was tolerated in this reaction (**3s**). Thienyl-substituted ynamide gave **3w** in 58% yield. As for the alkyl-substituted ynamide such as methyl-substituted one, the desired product **3x** could be formed in 21% yield, along with a byproduct **4**[20] derived from [2 + 2 + 2] cycloaddition of alkyne-nitrile with alkyne.[16]

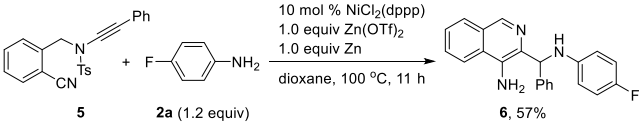
The reaction was also successfully expanded to ynamide-nitrile **5** linked by an alkylaryl group (Scheme 4). Interestingly, isoquinolin-4-amine **6** was obtained in 57% yield. Isoquinolin-

Scheme 3. Scope of the Ynamides[a]



[a]Isolated yields.

Scheme 4. Synthesis of Isoquinolin-4-amine Derivative



4-amine derivatives have recently been found to be an efficient NRF2 activator.[21] Unlike the product **3**, the imine part in **6** was reduced to an amine, indicating that possibly a Ni−H species was generated during the reaction.

To understand the reaction mechanism, we carried out the following experiments. First, we examined the reaction of **1a** and **2a** using a catalytic amount of $Ni(cod)_2$. Only a trace of **3a** was observed (Scheme 5, eq 1). However, in the presence of 1.0 equiv of Zn, **3a** could be formed in 21% yield. The results indicate that Zn may promote the regeneration of the Ni(0) catalyst. The use of a stoichiometric amount of $Ni(cod)_2$ and dppp gave the desired **3a** in 50% yield within 1 h. The yield was improved to 60% by adding 1.0 equiv of $Zn(OTf)_2$ (Scheme 5, eq 2). The results suggest that both the cyclization and desulfonylation processes can be catalyzed by a Ni(0) species.

Interestingly, preliminary results indicated that a highly efficient hydroamination of alkyl-substituted ynamide **5** could occur using 20% $Zn(OTf)_2$ as the catalyst, leading to **7** via α-addition (Scheme 5, eq 3). Such unwanted side reaction might compete with the main pathway, resulting in a lower yield of **6**.

Although the detailed mechanistic discussions should await further studies, we tentatively propose the following reaction mechanism for these reactions (Scheme 6). Initially, the in situ generated Ni(0) species coordinates with alkyne to form a π-

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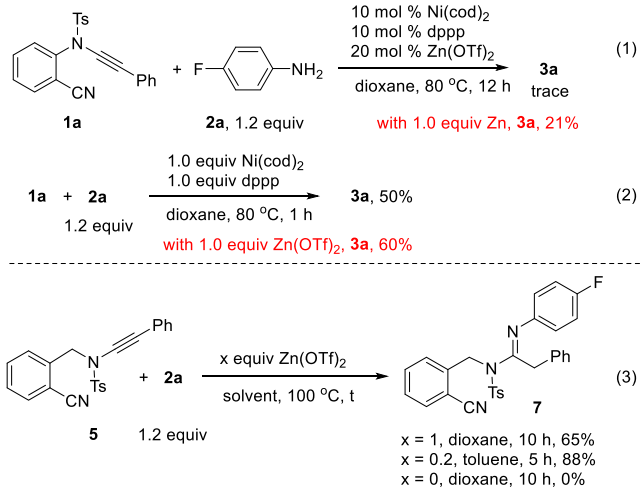
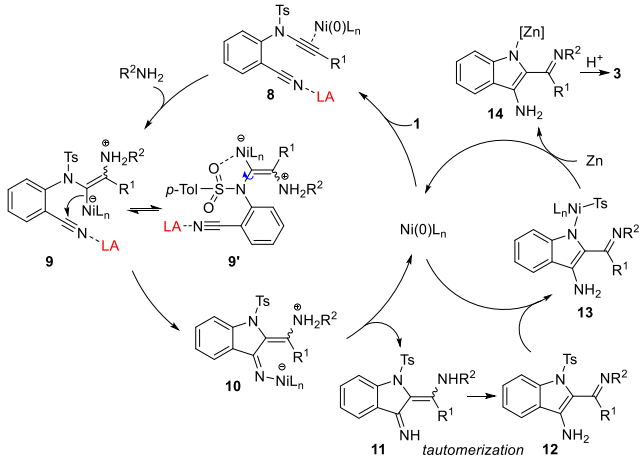
Scheme 5. Control Experiments



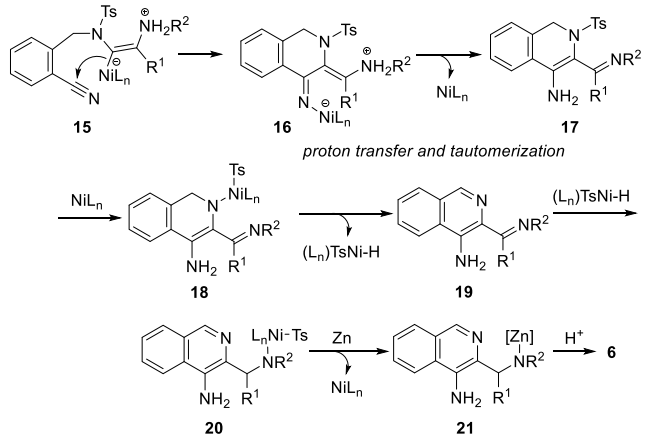
Scheme 6. Possible Mechanism for the Formation of 3



complex **8**. Regioselective addition of amine to the alkyne-complex **8** affords a zwitterion complex 9′ via *syn*- or *anti*-addition.[12d] The detailed mechanism and the stereochemistry for this addition process were not clear yet. The regioselectivity of this step might be ascribed to the chelation of the nickel catalyst with the tosyl group. The cyano group may also coordinate with nickel and direct the subsequent nucleophilic attack via **9** to give the cyclized intermediate **10**. Proton dissociation from the amino group and protonation of the iminium nickel species deliver intermediate **11**, which tautomerizes to afford intermediate **12**. Oxidative addition of *N*-Ts group in **12** to Ni(0) followed by reduction regenerates the Ni(0) species and forms the zinc intermediate **14**, which leads to the final product **3** upon protonation.[22] Alternatively, as suggested by a reviewer, the reaction might be initiated through N−H bond activation.[23] In this pathway, oxidative addition of the N−H bond in aniline by Ni(0) followed by Ni-amido bond addition to the alkyne affords a *syn*-alkenyl-Ni(II) species, or an *anti*-alkenyl-Ni(II) species via isomerization[24] of the *syn*-species. The subsequent step is similar to that shown in Scheme 6. The reaction pathway involving the azanickelacycle[16] could also not be excluded.

For the formation of **6** (Scheme 7), after cyclization, the oxidative addition of *N*-Ts to Ni(0) in **17** occurs followed by *β*-hydride elimination to give **19**. Then the hydride can reduce

Scheme 7. Possible Mechanism for the Formation of 6



the imine to form an amino-nickel(II) complex **20**, which undergoes reduction with Zn to provide zinc complex **21** and regenerates the Ni(0) catalyst.

In summary, a highly regioselective nickel-catalyzed cyclization of ynamide-nitriles with amines has been developed. The catalyst system, featured on the nickel and Lewis acid dual catalysis, offers an attractive and efficient route for the synthesis of 3-aminoindoles and 4-aminoisoquinoline derivatives which may have the potential utility in medicinal chemistry. The Ts-group on the ynamide acts as a directing group to produce the alkenyl nickel species with high regioselectivity. Further mechanistic studies and the development of the Ni-catalyzed transformations of ynamides are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04278.

Experimental details and spectroscopic characterization of all products and new substrates, Crystal data and structural refinement for compounds **3g**, **4**, **S-5** (2-tosylisoindolin-1-imine), **5**, **6**, and **7** (PDF)

Accession Codes

CCDC 2048276−2048278, 2056793, and 2057425−2057426 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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