JOC The Journal of Organic Chemistry

Article

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Palladium-Catalyzed Direct Arylation of C(sp^3)−H Bonds of α-Cyano Aliphatic Amides

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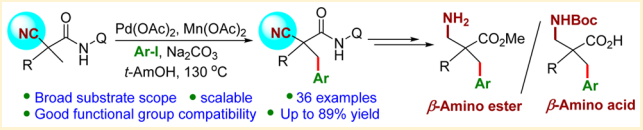
Supporting Information

ABSTRACT: Pd(OAc)$_2$-catalyzed arylation of C(sp^3)−H bonds in α-cyano-α-methyl aliphatic amides is achieved in the presence of 8-aminoquinoline, as a removable directing group, using Mn(OAc)$_2$ and Na$_2$CO$_3$. The current strategy enables the placement of an aryl/heteroaryl group at the β-position of α-cyano aliphatic acids for the first time. Wide functional group tolerance and easily accessible starting materials provide an efficient protocol for the synthesis of arylated α-cyano amides. Furthermore, the synthetic utility of the products has been demonstrated by their efficient conversions to medicinally important α,α-dialkylated acid and β-amino acid derivatives.

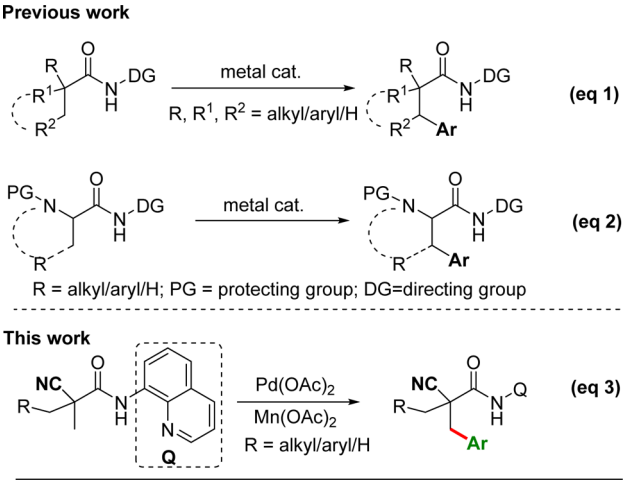


INTRODUCTION

Transition-metal-catalyzed functionalization of carbon−hydrogen bonds is an emerging topic in recent years.[1] The C−H bond activation protocol shortens the synthetic pathway and simplifies the retrosynthetic strategy by elimination of prefunctionalization of the starting materials. Over the years, functionalization of C(sp^2)−H bonds has developed as a means to construct carbon−carbon (C−C) and carbon−heteroatom (C−X) bonds. Significant work has been done in the area of unactivated C(sp^2)−H bond functionalization.[2] The construction of C−C and C−X bonds using unactivated C(sp^3)−H bonds, however, is a challenging task in modern synthetic and organometallic chemistry due to the ubiquity of C(sp^3)−H bonds in nature.[3] In this context, various transition-metal catalysts have been extensively utilized in metal-catalyzed C−H functionalizations. Among these, palladium complexes play a significant role in this field. More recently, a number of C(sp^3)−H bond to C(sp^3)−C and C(sp^3)−X bond transformations have been reported on carboxylic acid derivatives.[4−10] In particular, arylation of acyclic and cyclic aliphatic carboxylic acids[4] (Scheme 1, eq 1), amino acids[5] (Scheme 1, eq 2), and heterocyclic carboxylic acid derivatives[6] using a bidentate directing group have been reported, since a seminal article by Daugulis and co-workers in 2005.[4g] The pioneering work of the groups of Yu,[11] Chatani,[12] Daugulis,[4g] and others[13] has demonstrated that C(sp^3)−H bond functionalization could be accomplished through the use of an appropriate directing group. Despite developments in C(sp^3)−H bond functionalization of various acid derivatives, the functionalization of new classes of biologically significant synthons is beneficial, and further elucidation of this method is warranted.

2-Cyanoacetic acid derivatives are a class of active methylene compounds that can serve not only as versatile intermediates in pharmaceuticals and functional materials[14] but also as handy precursors in synthetic chemistry[15] due to their ability to undergo a broad range of functional group transformations.[16] Small molecules bearing a nitrile group comprise a considerable proportion of therapeutic drugs.[17] It is important to develop a substrate with diverse functional groups capable of further modification. Inspired by the pioneering work and our interest in C−H functionalization, we envisioned that the β-C(sp^3)−H bonds of cyanoacetic acid derivatives could undergo arylation with bidentate auxiliary assistance. Along this line, herein, we disclose the direct arylation of unactivated C(sp^3)−H bonds in α-cyano-α-methyl carboxylic acid amides using 8-aminoquinoline (Q) as a directing group with aryl/heteroaryl iodides under palladium catalysis (Scheme 1, eq 3).

Scheme 1. Transition-Metal-Catalyzed Arylation of Unactivated C(sp^3)−H Bonds of Aliphatic Amides



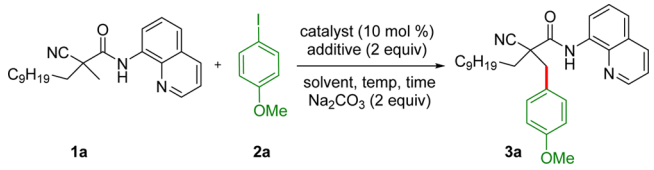
RESULTS AND DISCUSSION

We commenced our investigation with the reaction of 2-cyano-2-methyl-*N*-(quinolin-8-yl)dodecanamide (**1a**) (prepared from

Received: September 11, 2015
Published: October 29, 2015

DOI: 10.1021/acs.joc.5b02138
J. Org. Chem. 2015, 80, 11447−11459

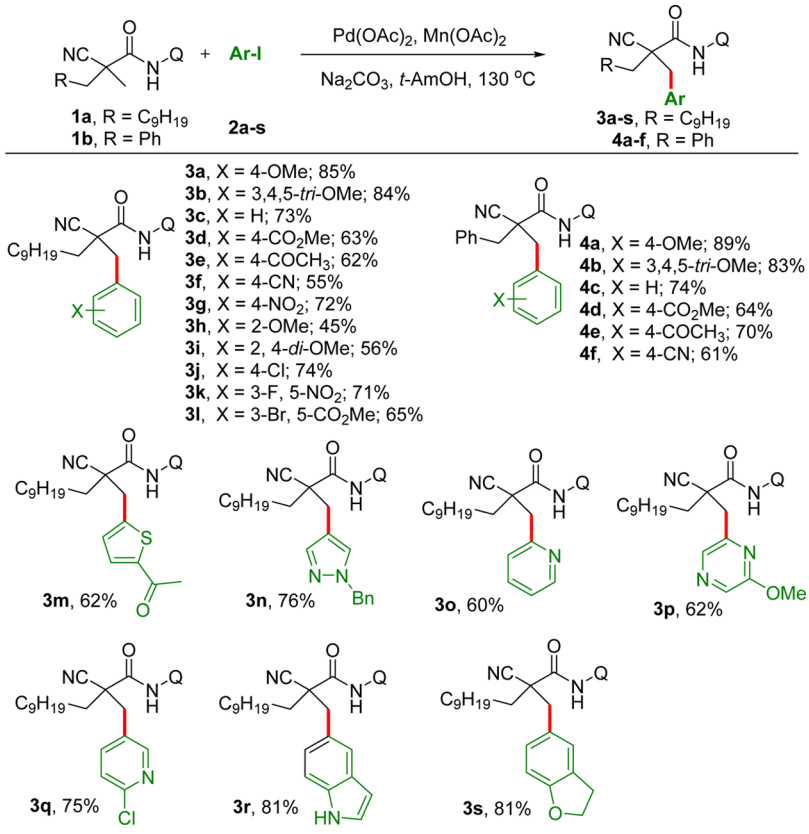
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	additive	solvent	temp (°C)	time (h)	yield (%)[b]
1	$Pd(OAc)_2$	AgOAc	toluene	120	24	18
2	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	130	24	15
3	$Pd(OAc)_2$	K_2S_2O8	toluene	130	24	trace
4	$Pd(OAc)_2$	$Mn(OAc)_2$	toluene	130	24	54
5	$Pd(OAc)_2$	$Mn(OAc)_2$	toluene	130	30	68
6	$Pd(OAc)_2$	$Mn(OAc)_2$	1,4-dioxane	130	30	72
7	$Pd(OAc)_2$	$Mn(OAc)_2$	CF_3CH_2OH	110	30	81
8	**$Pd(OAc)_2$**	**$Mn(OAc)_2$**	***t*-AmOH**	**130**	**30**	**85 (23,[c] 0[d])**
9	$Pd(OAc)_2$	$Mn(OAc)_2$	DCE	110	30	79
10	$Pd(TFA)_2$	$Mn(OAc)_2$	*t*-AmOH	130	30	51
11	$Pd(OPiv)_2$	$Mn(OAc)_2$	*t*-AmOH	130	30	46
12	$PdCl_2$	$Mn(OAc)_2$	*t*-AmOH	130	30	40

[a]Reaction conditions: cyanoamide **1a** (0.4 mmol), 4-iodoanisole (**2a**) (1.2 mmol), catalyst (10 mol %), additive (0.8 mmol), Na_2CO_3 (0.8 mmol), and solvent (4 mL). The optimal conditions are in bold. [b]All the products were characterized by ^1H and ^{13}C NMR, IR, and MS. [c]4-Bromoanisole used as aryl halide. [d]4-Chloroanisole used as aryl halide.

Scheme 2. Reactivity of Different Aryl/Heteroaryl Iodides with 1a and 1b[a]

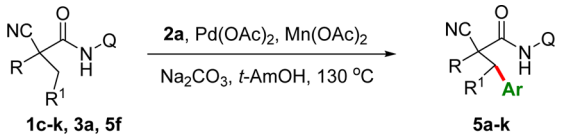


[a]Reaction conditions: cyanoamide **1** (0.4 mmol), iodoarene **2** (1.2 mmol), $Pd(OAc)_2$ (10 mol %), $Mn(OAc)_2$ (0.8 mmol), Na_2CO_3 (0.8 mmol), *t*-AmOH (4 mL), 130 °C, 30 h; all the products were characterized by ^1H and ^{13}C NMR, IR, and MS.

commercially available ethyl 2-cyanopropanoate with 1-bromodecane under K_2CO_3/CH_3CN conditions, followed by ester hydrolysis and amide formation; see Scheme 7) and 4-iodoanisole (**2a**), as a model substrate to establish the initial reaction parameters, in the presence of $Pd(OAc)_2$, Na_2CO_3 as base, and AgOAc as additive at 120 °C in toluene for 24 h (entry 1, Table 1). The expected monoarylated product **3a** was isolated, although in only 18% yield. We then examined the effects of various additives on product formation using $Pd(OAc)_2$ as catalyst and either $Cu(OAc)_2$, $K_2S_2O_8$, or

DOI: 10.1021/acs.joc.5b02138
J. Org. Chem. 2015, 80, 11447−11459

Table 2. Arylation of Various α-Cyanoacetic Acid Derivatives with 2a[a]



1c-k, 3a, 5f 5a-k

entry	α-cyanoamide	product (5)	yield[a]
1	**1c**, R = *n*-C_5H_{11}–, R^1 = H	**5a**, R = *n*-C_5H_{11}–, R^1 = H	77
2	**1d**, R = *n*-$C_{16}H_{33}$–, R^1 = H	**5b**, R = *n*-$C_{16}H_{33}$–, R^1 = H	83
3	**1e**, R = cyclohexylmethylene, R^1 = H	**5c**, R = cyclohexylmethylene, R^1 = H	78
4	**1f**, R = $PhCH_2$–, R^1 = H	**5d**, R = $PhCH_2$–, R^1 = H	82
5	**1g**, R = $Ph(CH_2)_2$–, R^1 = H	**5e**, R = $Ph(CH_2)_2$–, R^1 = H	84
6	**1h**, R = CH_3, R^1 = H	**5f**, R = CH_3, R_1 = H	50[b]
7	**5f**, R = 4-MeO–C_6H_4–, R^1 = H	**5g**, R = 4-MeO–C_6H_4–, R^1 = H	86
8	**1i**, R = *i*-Bu, R^1 = H	**5h**, R = *i*-Bu, R^1 = H	81
9	**1j**, R = H, R^1 = $PhCH_2$–	**5i**, R = H, R^1 = $PhCH_2$–	0[c]
10	**1k**, R = H, R^1 = C_9H_{19}–	**5j**, R = H, R^1 = C_9H_{19}–	0[d]
11	**3a**, R = $C_{10}H_{21}$–, R^1 = 4-MeO–C_6H_4–	**5k**, R = $C_{10}H_{21}$-, R^1 = –4-MeO–C_6H_4–	20[e]

[a]Reaction conditions: α-cyanoamide (0.4 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$ (10 mol %), $Mn(OAc)_2$ (0.8 mmol), Na_2C0_3 (0.8 mmol), *t*-AmOH (4 mL), 130 °C, 30 h; Ar– = 4-MeO–C_6H_4–. All the products were characterized by ^1H, ^{13}C NMR, IR and MS. [b]Diarylated product **5g** also formed in 29% yield. [c]45% of **1j** was recovered. [d]89% of **1k** was recovered. [e]0.1 mmol of **3a**, 0.15 mmol of **2a** were used.

$Mn(OAc)_2$ at 130 °C in toluene for 24 h. Unsatisfactory yields were obtained with $Cu(OAc)_2$ as well as $K_2S_2O_8$ (entries 2 and 3). However, $Mn(OAc)_2$ greatly aided the conversion of **1a**, affording **3a** in 54% yield (entry 4). This is significant, since iodide scavenging is accomplished without the need for silver salts. Next, prolongation of the reaction time with $Pd(OAc)_2$ and $Mn(OAc)_2$ in toluene resulted in **3a** in 68% yield (entry 5). Subsequently, on the basis of the screening of a series of solvents, including 1,4-dioxane, CF_3CH_2OH, *t*-AmOH, and 1,2-dichloroethane, with $Pd(OAc)_2$ and $Mn(OAc)_2$ at different temperatures for 30 h (entries 6–9), we concluded that *t*-AmOH was the solvent of choice, providing **3a** in 85% yield (entry 8, Table 1). In addition, employing coupling partners such as 4-bromoanisole (23%) or 4-chloroanisole (no reaction) instead of **2a** was ineffective (entry 8, Table 1), and replacing $Pd(OAc)_2$ with $Pd(TFA)_2$, $Pd(OPiv)_2$, or $PdCl_2$ resulted in lower yields (entries 10–12). From the series of above examinations, the combination of 10 mol % of $Pd(OAc)_2$, $Mn(OAc)_2$ (2 equiv), and Na_2CO_3 (2 equiv) in *t*-AmOH at 130 °C for 30 h was determined to be the optimal reaction conditions.[18]

We next examined the scope and generality of an extensive range of aryl iodides with α-cyano amides **1a** and **1b** using the optimized conditions. Results are summarized in Scheme 2. Substrates with electron-donating and -withdrawing substituents are well-tolerated under the optimal reaction conditions. The 4-OMe and 3,4,5-tri-OMe iodobenzene derivatives (**2a** and **2b**) reacted cleanly to give the corresponding products in excellent yields (**3a** and **3b**). Iodobenzene **2c** was also subjected to the optimized conditions and provided the corresponding product (**3c**) in 73% yield.

Diverse electron-withdrawing groups on the aryl iodide (**2d**–**2g**, 4-CO_2Me, 4-$COCH_3$, 4-CN, and 4-NO_2) were all well-tolerated with **1a** to give the appropriate products in moderate to good yields (**3d**–**3g**). Importantly, ortho-substituted aryl iodides [2-OMe (**2h**) and 2,4-di-OMe (**2i**)] were also compatible in the present protocol to afford the desired products in moderate to low yields (**3h** and **3i**), presumably due to steric effects. The 4-chloro-, 3-fluoro-5-nitro-, and 3-bromo-5-methylcarboxylate aryl iodides (**2j**–**2l**) successfully gave the corresponding arylated products (**3j**–**3l**) with reasonably good yields from **1a**. Moreover, α-cyano amide derivative **1b** was also tested under these optimal conditions, with aryl iodides (**2a**–**2f**) bearing electron-rich and -poor groups, to afford the corresponding products in good yields (**4a**–**4f**). Auspiciously, the reaction of diverse heteroaromatic iodides (**2m**–**2s**) with **1a** smoothly furnished the corresponding heteroaryl-substituted α-cyano amides in synthetically useful yields: substituted thiophene-amide (**3m**, 62%), 1-benzyl-1*H*-pyrazole-amide (**3n**, 76%), 2-pyridine-amide (**3o**, 60%), 6-methoxypyrazine-amide (**3p**, 62%), 2-chloropyridine-amide (**3q**, 75%), *N*-unprotected indole-amide (**3r**, 81%), and 2,3-dihydrobenzofuran-amide (**3s**, 79%), respectively. It is noteworthy to mention here that the obtained products provide a critical handle for further structural elaboration.

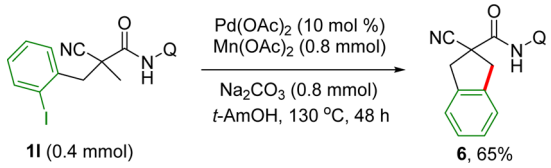
A variety of α-cyano carboxylic acid derivatives were successfully arylated with 8-aminoquinoline as a directing group under the optimal reaction conditions with **2a** (Table 2). α-Cyano amides bearing aliphatic long chains (**1c** and **1d**) were well-tolerated to afford the corresponding products **5a** and **5b** in excellent yields. 2-Cyano-3-cyclohexylpropanamide derivative **1e** was coupled with **2a** to give **5c** in 78% yield, while 4-phenylbutaramide (**1f**) and 5-phenylpentanamide (**1g**) derivatives afforded the arylated products **5d** and **5e**, respectively, in good yields. Interestingly, 2-cyano-2-methyl-*N*-(quinolin-8-yl)-propanamide (**1h**), treated with **2a** under palladium-catalyzed conditions, furnished a mixture of monoarylated amide (**5f**) in 50% and diarylated amide (**5g**) in 29% yields. Further, the monoarylated product (**5f**) was treated separately with **2a** under optimal conditions to afford **5g** in 86% yield. α-Cyano-2,5-dimethyl amide analog (**1i**) gave the arylated **5h** in 81% yield. We further examined the utility of this method by examining the reactivity of monomethylene systems at the β-position (**1j** and **1k**). Treatment of **1j** or **1k** with **2a** under standard reaction conditions failed to give the arylated products (**5i** and **5j**, respectively), presumably due to an active C–H proton at the α-position of the substrates. Only starting materials were recovered from the reaction. Interestingly, the reaction of **3a** (containing two methylene systems at the β-position, 0.1 mmol) and **2a** (0.15 mmol) did afford the

DOI: 10.1021/acs.joc.5b02138
J. Org. Chem. 2015, 80, 11447–11459

corresponding monoarylated product **5k** at the benzylic position, although in only 20% yield.

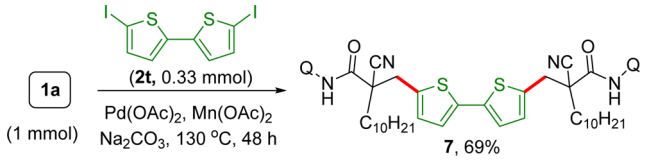
Encouraged by the successful utilization of various aryl iodides and α-cyanoamide derivatives for palladium-catalyzed C(sp^3)−H functionalization, we turned our attention to the more challenging intramolecular C(sp^3)−H arylation reaction (Scheme 3). We prepared an α-cyano substrate [2-cyano-3-(2-iodophenyl)-2-methyl-*N*-(quinolin-8-yl)propanamide), **1l**] embedded with an iodoarene and treated it with 10 mol % $Pd(OAc)_2$, $Mn(OAc)_2$ (2 equiv), and Na_2CO_3 (2 equiv) in *t*-AmOH at 130 °C for 48 h. The reaction proceeded smoothly to give the 2-cyano-2,3-dihydro-1*H*-indene-2-carboxamide derivative (**6**) in 65% yield.

Scheme 3. Intramolecular C(sp^3)−H Arylation Reaction



Next, we used 5,5′-diiodo-2,2′-bisthiophene (**2t**) as an aryl iodide to test the structural generality of the reaction under the optimized conditions, as shown in Scheme 4. The reaction of **1a** (3 mmol) with **2t** (1 mmol) proceeded smoothly to give the difunctionalized product (**7**) in 69% yield.

Scheme 4. Arylation of 1a with Diiodobisthiophene



Remarkably, we also successfully applied the current protocol to the gram-scale synthesis of arylated compounds **3a** and **4a** using 4 mmol of **1a** and **1b**, separately, under the optimal conditions with **2a**, resulting in 1.36 g of **3a** (72%) and 1.26 g of **4a** (75%), respectively (Scheme 5). The synthetic usefulness of these representative compounds was demonstrated through various functional group transformations. Initially, elimination of the nitrile group in **4a** resulted in the dialkylated amide (**8**) in 45% yield. We also found that **4a** under strongly basic conditions led to hydrolysis of both nitrile and amide groups, followed by decarboxylation of the acid functional group to afford the α,α-disubstituted amide (**9a**) in 77% yield and the acid (**9b**) in 65% yield with longer reaction time. Additionally, in both compounds **3a** and **4a**, the auxiliary 8-aminoquinoline group was easily removed using KOH/*t*-AmOH conditions to generate versatile acid motifs **10a** (79%) and **10b** (75%) in good yields, while the nitrile group remained intact. Similarly, removal of the auxiliary in **3a** and **4a** using HCl/MeOH reflux conditions gave the corresponding methyl esters in excellent yields (**11a**, **11b**). Interestingly, cyano acids **10a** and **10b** or cyano esters **11a** and **11b** could be subjected to hydrogenation (Pd−C in MeOH) to give the corresponding *N*-Boc-β-amino acids, **12a** (59%) and **12b** (55%), or β-amino esters, **13a** (82%) and **13b** (80%), respectively.

To further elaborate the applicability of the obtained products, compound **4c** was subjected to $LiAlH_4$ to provide the 1,3-amino alcohol **14** in 72% yield (Scheme 6).

CONCLUSION

In summary, we have developed an 8-aminoquinoline-directed arylation of unactivated C(sp^3)−H bonds of α-cyano aliphatic amides with aryl/heteroaryl iodides under palladium catalysis. The reaction offers wide functional group compatibility and broad substrate scope (including heterocyclic substrates) and provides arylated α-cyano amides in good to excellent yields, even on gram scale. The obtained products can be utilized for the development of various synthetically useful compounds and privileged motifs in pharmaceuticals, such as disubstituted α-cyano acids, α,α-dialkylated acid derivatives, β-amino acid derivatives, and amino alcohols. Further applications of this method are underway in our laboratory.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. All reactions were conducted in glassware that was dried in an oven (120 °C), heated under reduced pressure, and cooled under a stream of argon before use. Reactions were monitored by thin-layer chromatography on silica gel plates using UV light (254 nm) and ceric sulfate or β-naphthol for visualization. Column chromatography was performed on a flash chromatography system with silica gel columns using *n*-hexane and ethyl acetate as eluent. Evaporation of solvents was conducted under reduced pressure at 50 °C using rotary evaporators. FTIR spectra were recorded neat, and wavenumbers are indicated in cm^{-1}. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C). Deuterated chloroform was used as the solvent, and spectra were calibrated against the residual solvent peak at 7.26 ppm for ^{1}H and at 77.0 ppm for ^{13}C or against TMS. Chemical shifts (δ) and coupling constants (*J*) are given in ppm (parts per million) and Hz (Hertz), respectively. The following abbreviations are used to describe the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad singlet. Low-resolution mass spectra were obtained by electrospray ionization (ESI) in positive mode. High-resolution mass spectra (HRMS) were performed with an orbitrap mass analyzer by electrospray ionization (ESI).

General Procedure for the Preparation of Starting Materials.[19] To a solution of ethyl 2-cyanopropionate (635 mg, 0.629 mL, 5 mmol) in acetonitrile (20 mL) were added K_2CO_3 (1.38 g, 10 mmol) and alkyl halide (6 mmol). After the addition, the mixture was warmed to 70 °C and stirred overnight. The mixture was cooled to room temperature (rt), and the solvent was removed under vacuum. Water (20 mL) was added and the product extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under vacuum. The crude residue was purified by flash column chromatography to provide the corresponding ester. The ester was dissolved in THF (15 mL) and treated with a solution of NaOH (800 mg, 20 mmol, 9 mL of water). The mixture was stirred at rt for 12 h. After removal of THF in vacuo, the pH of the aqueous layer was adjusted to 4.0 with 2.0 M HCl. The mixture was extracted with DCM (20 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give the crude carboxylic acid, which was used in the next reaction without further purification.

$SOCl_2$ (0.51 mL, 7 mmol) was added slowly to a stirred solution of the carboxylic acid in toluene (15 mL) and DMF (0.1 mL) at room temperature. The mixture was stirred for 3 h at 110 °C and the solvent evaporated in vacuo. The residue was then dissolved in toluene (5 mL) and evaporated in vacuo twice to give the crude acid chloride. The acid chloride was added dropwise to a solution of 8-aminoquinoline (720 mg, 5 mmol) and DIPEA (1.26 g, 1.74 mL, 10 mmol) in CH_2Cl_2 (20 mL) at −10 °C over 15 min. The resulting solution was warmed to rt

DOI: 10.1021/acs.joc.5b02138
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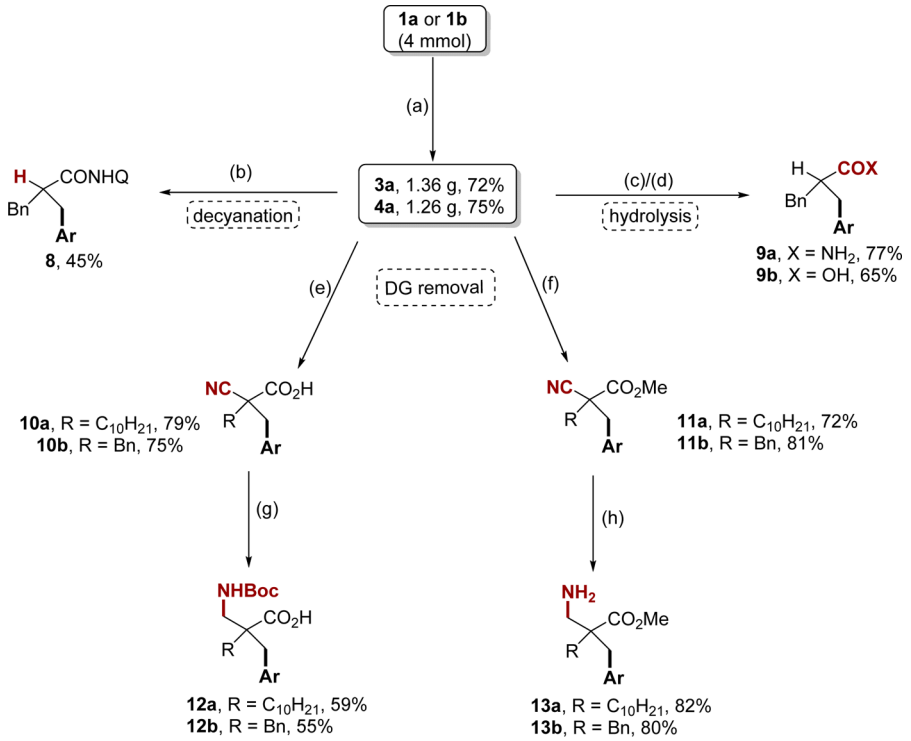
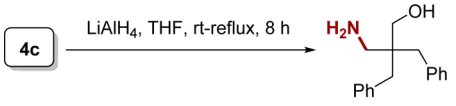
Scheme 5. Gram-Scale Syntheses of 3a and 4a and Their Synthetic Utility[a]



[a]Reaction conditions: (a) **2a**, $Pd(OAc)_2$, $Mn(OAc)_2$, Na_2CO_3, *t*-AmOH, 130 °C, 30 h. (b) SmI_2, HMPA, THF, 0 °C−rt, 6 h. (c) KOH, *t*-AmOH, 120 °C, 24 h. (d) KOH, *t*-AmOH, 130 °C, 40 h. (e) KOH, *t*-AmOH, 90 °C, 3 h. (f) HCl, MeOH, reflux, 20 h. (g) 10% Pd−C, H_2, $(Boc)_2O$, DIPEA, MeOH, rt, 36−40 h. (h) 10% Pd−C, H_2, HCl, MeOH, rt, 24 h.

Scheme 6. Synthesis of 1,3-Amino Alcohol 14



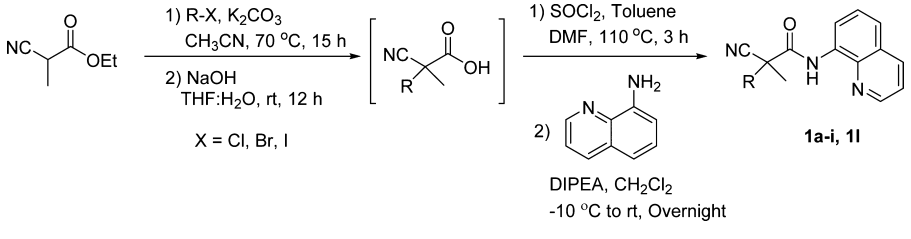
and stirred overnight. The mixture was diluted with CH_2Cl_2 (15 mL) and washed successively with water (20 mL), saturated aqueous $NaHCO_3$ (20 mL), HCl (0.5 M, 20 mL), and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexane (1:9, v/v), to afford the corresponding 2-cyano-2-methyl-8-aminoquinolinylamides **1** (Scheme 7).

*2-Cyano-2-methyl-N-(quinolin-8-yl)dodecanamide (**1a**).* 1-Bromodecane (1.32 g, 1.23 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a brown oil (1.44 g, 79%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.88 (s, 1H), 8.89 (dd, J = 4.2, 2.4 Hz, 1H), 8.75 (dd, J = 7.1, 1.8 Hz, 1H), 8.19 (dd, J = 8.3, 1.6 Hz, 1H), 7.60−7.53 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 2.13 (td, J = 12.3, 4.5 Hz, 1H), 1.85 (td, J = 12.2, 4.5 Hz, 1H), 1.74 (s, 3H), 1.68−1.57 (m, 1H), 1.51−1.40 (m, 1H), 1.38−1.20 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.6, 148.9, 138.8, 136.2, 133.5, 127.9, 127.1, 122.7, 121.9, 121.4, 116.7, 45.5, 38.6, 31.8, 29.5, 29.4, 29.3, 29.3, 29.2, 25.6, 24.1, 22.6, 14.1; FTIR (neat) 3307, 2924, 2853, 2235, 1688, 1529, 1486, 1424, 1327, 1132, 1057, 825, 791, 698 cm^{-1}; MS (ESI) m/z 366 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{23}H_{32}ON_3$ $(M + H)^+$ 366.2540, found 366.2539.

*2-Cyano-2-methyl-3-phenyl-N-(quinolin-8-yl)propanamide (**1b**).* Benzyl bromide (1.02 g, 0.71 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a brown solid (1.27 g, 81%): mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.79 (dd, J = 4.2, 1.7 Hz, 1H), 8.71 (dd, J = 6.3, 2.7 Hz, 1H), 8.14 (dd, J = 8.3, 1.6 Hz, 1H), 7.57−7.51 (m, 2H), 7.44 (dd, J = 8.3, 4.2 Hz, 1H), 7.38−7.33 (m, 2H), 7.30−7.18 (m, 3H), 3.44 (d, J = 13.5 Hz, 1H), 3.12 (d, J = 13.5 Hz, 1H), 1.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.6, 148.8, 138.7, 136.1, 134.5, 133.5, 130.1, 130.0, 128.6, 127.8, 127.0, 122.7, 121.9, 120.9, 116.7, 46.9, 43.9, 23.7; FTIR (neat) 3275, 3028, 2928, 2234, 1687, 1539, 1485, 1331, 1205, 1174, 1072, 882, 792, 699 cm^{-1}; MS (ESI) m/z 316 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{20}H_{18}ON_3$ $(M + H)^+$ 316.1444, found 316.1440.

*2-Cyano-2-methyl-N-(quinolin-8-yl)heptanamide (**1c**).* 1-Iodopentane (1.18 g, 0.781 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a dark brown oil (1.06 g, 72%): ^{1}H

Scheme 7. Preparation of Starting Compounds 1a−1i, 1l



DOI: 10.1021/acs.joc.5b02138
J. Org. Chem. 2015, 80, 11447−11459

NMR (400 MHz, $CDCl_3$) δ 10.89 (s, 1H), 8.89 (dd, J = 4.2, 1.6 Hz, 1H), 8.72 (dd, J = 7.1, 1.8 Hz, 1H), 8.19 (dd, J = 8.2, 1.6 Hz, 1H), 7.60−7.53 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 2.13 (td, J = 12.3, 4.5 Hz, 1H), 1.87 (td, J = 12.3, 4.5 Hz, 1H), 1.74 (s, 3H), 1.70−1.57 (m, 1H), 1.52−1.42 (m, 1H), 1.36−1.28 (m, 4H), 0.87 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 148.8, 138.8, 136.2, 133.6, 127.9, 127.1, 122.6, 121.9, 121.4, 116.7, 45.5, 38.5, 31.4, 25.3, 24.1, 22.3, 13.9; FTIR (neat) 3274, 3062, 2929, 2234, 1687, 1537, 1486, 1266, 1174, 1072, 824, 792, 699 cm^{-1}; MS (ESI) m/z 296 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{18}H_{22}ON_3$, $(M + H)^+$ 296.1757, found 296.1753.

*2-Cyano-2-methyl-N-(quinolin-8-yl)octadecanamide (**1d**).* 1-Bromohexadecane (1.83 g, 1.83 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a pale yellow solid (1.84 g, 82%): mp 48−49 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.88 (s, 1H), 8.89 (dd, J = 4.2, 1.7 Hz, 1H), 8.72 (dd, J = 7.1, 1.8 Hz, 1H), 8.19 (dd, J = 8.3, 1.6 Hz, 1H), 7.60−7.53 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 2.13 (td, J = 12.3, 4.5 Hz, 1H), 1.86 (td, J = 12.3, 4.4 Hz, 1H), 1.74 (s, 3H), 1.68−1.58 (m, 1H), 1.52−1.41 (m, 1H), 1.39−1.19 (m, 26H), 0.87 (t, J = 13.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 148.9, 138.8, 136.2, 133.6, 127.9, 127.1, 122.6, 121.9, 121.4, 116.7, 45.5, 38.6, 31.9, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.5, 29.5, 29.4, 29.3, 29.2, 25.6, 24.1, 22.7, 14.1; FTIR (neat) 3306, 2914, 2850, 2230, 1709, 1693, 1532, 1466, 1330, 1151, 822, 782 cm^{-1}; MS (ESI) m/z 450 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{29}H_{44}ON_3$ $(M + H)^+$ 450.3479, found 450.3482.

*2-Cyano-3-cyclohexyl-2-methyl-N-(quinolin-8-yl)propanamide (**1e**).* (Bromomethyl)cyclohexane (1.06 g, 0.834 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a pale yellow oil (1.25 g, 78%): ^1H NMR (400 MHz, $CDCl_3$) δ 10.93 (s, 1H), 8.89 (dd, J = 4.2, 1.6 Hz, 1H), 8.71 (dd, J = 7.1, 1.8 Hz, 1H), 8.18 (dd, J = 8.3, 1.6 Hz, 1H), 7.60−7.52 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 2.13 (dd, J = 14.7, 7.2 Hz, 1H), 1.91 (d, J = 12.8 Hz, 1H), 1.79−1.53 (m, 8H), 1.30−0.93 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 148.9, 138.8, 136.2, 133.6, 127.9, 127.1, 122.6, 121.9, 121.7, 116.7, 45.3, 44.1, 35.4, 34.0, 33.0, 26.0, 25.9, 25.9, 25.8; FTIR (neat) 3308, 2922, 2850, 2234, 1690, 1526, 1424, 1326, 1260, 1132, 922, 825, 755 cm^{-1}; MS (ESI) m/z 322 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{20}H_{24}ON_3$ $(M + H)^+$ 322.1914, found 322.1915.

*2-Cyano-2-methyl-4-phenyl-N-(quinolin-8-yl)butanamide (**1f**).* (2-Bromoethyl)benzene (1.11 g, 0.82 mL, 6 mmol) used as the alkyl halide and the product was obtained as a pale yellow oil (1.40 g, 85%): ^1H NMR (400 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.90 (dd, J = 5.8, 2.6 Hz, 1H), 8.72 (dd, J = 7.2, 1.7 Hz, 1H), 8.19 (dd, J = 8.3, 1.6 Hz, 1H), 7.61−7.53 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 7.28−7.14 (m, 5H), 2.94 (td, J = 12.6, 4.8 Hz, 1H), 2.79 (td, J = 12.6, 5.0 Hz, 1H), 2.57 (td, J = 12.4, 5.0 Hz, 1H), 2.13 (td, J = 12.6, 4.8 Hz, 1H), 1.79 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 148.9, 139.8, 138.7, 136.2, 133.4, 128.5, 128.4, 127.8, 127.0, 126.3, 122.8, 121.9, 121.1, 116.8, 45.3, 40.3, 32.0, 24.4; FTIR (neat) 3306, 3029, 2934, 2233, 1687, 1527, 1485, 1326, 1261, 1156, 1055, 790, 697 cm^{-1}; MS (ESI) m/z 330 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{21}H_{20}ON_3$ $(M + H)^+$ 330.1601, found 330.1602.

*2-Cyano-2-methyl-5-phenyl-N-(quinolin-8-yl)pentanamide (**1g**).* (3-Bromopropyl)benzene (1.19 g, 0.915 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a pale yellow oil (1.39 g, 81%): ^1H NMR (400 MHz, $CDCl_3$) δ 10.88 (s, 1H), 8.86 (dd, J = 4.2, 1.6 Hz, 1H), 8.71 (dd, J = 7.0, 1.9 Hz, 1H), 8.15 (dd, J = 8.3, 1.6 Hz, 1H), 7.58−7.50 (m, 2H), 7.46 (dd, J = 8.3, 4.2 Hz, 1H), 7.27−7.22 (m, 2H), 7.19−7.13 (m, 3H), 2.78−2.61 (m, 2H), 2.22−2.14 (m, 1H), 2.02−1.76 (m, 3H), 1.72 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 148.8, 141.0, 138.7, 136.2, 133.5, 128.4, 128.3, 127.8, 127.0, 126.0, 122.7, 121.9, 121.3, 116.7, 45.3, 38.0, 35.3, 27.2, 24.1; FTIR (neat) 3308, 3063, 2935, 2962, 2235, 1687, 1527, 1485, 1326, 1262, 1132, 1029, 929, 825, 750 cm^{-1}; MS (ESI) m/z 344 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{22}H_{22}ON_3$ $(M + H)^+$ 344.1757, found 344.1764.

*2-Cyano-2-methyl-N-(quinolin-8-yl)propanamide (**1h**).* Iodomethane (0.85 g, 0.373 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a brown oil (0.78 g, 65%): ^1H NMR (400 MHz, $CDCl_3$) δ 10.81 (s, 1H), 8.88 (dd, J = 4.2, 1.7 Hz, 1H), 8.70 (dd, J = 7.0, 1.9 Hz, 1H), 8.19 (dd, J = 8.3, 1.6 Hz, 1H), 7.60−7.52 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 1.78 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 148.8, 138.7, 136.3, 133.6, 127.9, 127.1, 122.7, 122.0, 121.9, 116.7, 40.0, 25.3; FTIR (neat) 3276, 2984, 2235, 1686, 1531, 1485, 1424, 1327, 1243, 1156, 918, 899, 791, 640 cm^{-1}; MS (ESI) m/z 240 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{14}H_{14}ON_3$ $(M + H)^+$ 240.1131, found 240.1132.

*2-Cyano-2,5-dimethyl-N-(quinolin-8-yl)hexanamide (**1i**).* 1-Bromo-3-methylbutane (0.91 g, 0.758 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a pale yellow oil (1.16 g, 79%): ^1H NMR (400 MHz, $CDCl_3$) δ 10.89 (s, 1H), 8.89 (dd, J = 5.8, 2.6 Hz, 1H), 8.73 (dd, J = 7.1, 1.8 Hz, 1H), 8.13 (dd, J = 8.2, 1.6 Hz, 1H), 7.60−7.52 (m, 2H), 7.48 (dd, J = 8.3, 4.2 Hz, 1H), 2.14 (td, J = 12.3, 4.6 Hz, 1H), 1.85 (td, J = 12.8, 4.4 Hz, 1H), 1.75 (s, 3H), 1.65−1.55 (m, 1H), 1.54−1.47 (m, 1H), 1.41−1.31 (m, 1H), 0.91 (dd, J = 6.5, 3.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 148.8, 138.8, 136.2, 133,6, 127.8, 127.1, 122.6, 121.9, 121.4, 116.7, 45.5, 36.6, 34.3, 28.0, 24.1, 22.4; FTIR (neat) 3310, 2956, 2870, 2235, 1688, 1527, 1486, 1466, 1326, 1154, 918, 825, 790, 755 cm^{-1}; MS (ESI) m/z 296 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{18}H_{22}ON_3$ $(M + H)^+$ 296.1757, found 296.1753.

*2-Cyano-3-(2-iodophenyl)-2-methyl-N-(quinolin-8-yl)-propanamide (**1l**).* 2-Iodobenzyl bromide (1.78 g, 6 mmol) was used as the alkyl halide and the product was obtained as a pale yellow oil (1.65 g, 75%): ^1H NMR (400 MHz, $CDCl_3$) δ 10.80 (s, 1H), 8.79 (dd, J = 5.8, 2.5 Hz, 1H), 8.75 (dd, J = 6.4, 2.5 Hz, 1H), 8.16 (dd, J = 8.3, 1.6 Hz, 1H), 7.84 (dd, J = 7.9, 1.2 Hz, 1H), 7.60−7.53 (m, 2H), 7.48−7.43 (m, 2H), 7.25 (dd, J = 7.5, 1.2 Hz, 1H), 6.91 (dd, J = 7.7, 1.6 Hz, 1H), 3.62 (d, J = 14.2 Hz, 1H), 3.52 (d, J = 14.2 Hz, 1H), 1.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 148.7, 140.1, 138.7, 137.8, 136.1, 133.4, 130.4, 130.3, 129.4, 128.5, 127.8, 127.0, 122.7, 121.8, 120.7, 116.7, 102.6, 46.4, 23.7; FTIR (neat) 3299, 3050, 2988, 2236, 1686, 1527, 1485, 1326, 1241, 1126, 1012, 904, 789 cm^{-1}; MS (ESI) m/z 442 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{20}H_{17}ION_3$ $(M + H)^+$ 442.0411, found 442.0416.

*2-Cyano-4-phenyl-N-(quinolin-8-yl)butanamide (**1j**).* To a solution of ethyl 2-cyanoacetate (565 mg, 0.538 mL, 5 mmol) in acetonitrile (20 mL) were added K_2CO_3 (138 mg, 1 mmol) and (2-bromoethyl)benzene (185 mg, 0.14 mL, 1 mmol). After the addition, the mixture was warmed to 70 °C and stirred overnight. The mixture was cooled to rt, and the solvent was removed under vacuum. Water (20 mL) was added and the product extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude residue was purified by flash column chromatography to provide the corresponding ester. The ester was dissolved in THF (5 mL) and treated with a solution of NaOH (160 mg, 4 mmol, 3 mL of water). The mixture was stirred at rt for 12 h. After removal of THF in vacuo, the pH of the aqueous layer was adjusted to 4.0 with 2.0 M HCl. The mixture was extracted with DCM (10 mL × 2). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and evaporated to give the crude carboxylic acid, which was used in the next reaction without further purification.

A mixture of the crude 2-cyano-4-phenylbutanoic acid (190 mg, 1 mmol), 8-aminoquinoline (145 mg, 1 mmol), EDCI (163 mg, 1.05 mmol), HOBt·H_2O (161 mg, 1.05 mmol), and DIPEA (387 mg, 3 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred at rt overnight. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with EtOAc/hexane (1:9, v/v), to give the title compound **1j** as a brown solid (233 mg, 74% yield): mp 62−63 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.68 (dd, J = 7.2, 1.7 Hz, 1H), 8.18 (dd, J = 8.3, 1.6 Hz, 1H), 7.59−7.50 (m, 2H), 7.48 (dd, J = 8.3, 4.2 Hz, 1H), 7.34−7.19 (m, 5H), 3.65 (dd, J = 8.5, 5.9 Hz, 1H), 3.03−2.84 (m, 2H), 2.54−2.37 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.6, 148.6, 139.2, 138.3, 136.5, 133.3, 128.7, 128.6, 127.8, 127.1, 126.7,

DOI: 10.1021/acs.joc.5b02138
J. Org. Chem. 2015, 80, 11447−11459

122.8, 121.9, 117.5, 116.9, 38.9, 32.8, 31.8; FTIR (neat) 3308, 2925, 2853, 2250, 1667, 1536, 1499, 1322, 1239, 827, 790 cm^{-1}; MS (ESI) m/z 316 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{20}H_{18}ON_3$ $(M + H)^+$ 316.1444, found 316.1445.

*2-Cyano-N-(quinolin-8-yl)dodecanamide (**1k**).* To a solution of ethyl 2-cyanoacetate (565 mg, 0.538 mL, 5 mmol) in acetonitrile (20 mL) were added K_2CO_3 (138 mg, 1 mmol) and 1-bromodecane (220 mg, 0.20 mL, 1 mmol). After the addition, the mixture was warmed to 70 °C and stirred overnight. The mixture was cooled to rt, and the solvent was removed under vacuum. Water (20 mL) was added and the product extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated under vacuum. The crude residue was purified by flash column chromatography to provide the corresponding ester. The ester was dissolved in THF (5 mL) and treated with a solution of NaOH (160 mg, 4 mmol, 3 mL of water). The mixture was stirred at rt for 12 h. After removal of THF in vacuo, the pH of the aqueous layer was adjusted to 4.0 with 2.0 M HCl. The mixture was extracted with DCM (10 mL × 2). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and evaporated in vacuo to give the crude carboxylic acid, which was used in the next reaction without further purification.

A mixture of the crude 2-cyanododecanoic acid (225 mg, 1 mmol), 8-aminoquinoline (145 mg, 1 mmol), EDCI (163 mg, 1.05 mmol), HOBt·H_2O (161 mg, 1.05 mmol), and DIPEA (387 mg, 3 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred at rt overnight. Water was added and the mixture was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with EtOAc/hexane (1:9, v/v), to give the title compound **1k** as a brown solid (245 mg, 70% yield): mp 89–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.85 (dd, J = 4.2, 1.6 Hz, 1H), 8.69 (dd, J = 7.0, 1.8 Hz, 1H), 8.17 (dd, J = 8.2, 1.6 Hz, 1H), 7.60–7.51 (m, 2H), 7.48 (dd, J = 8.3, 4.2 Hz, 1H), 3.70 (dd, J = 7.6, 6.4 Hz, 1H), 2.19–2.07 (m, 2H), 1.67–1.54 (m, 2H), 1.43–1.20 (m, 14H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.9, 148.7, 138.5, 136.3, 133.4, 127.8, 127.3, 122.7, 121.9, 117.8, 116.8, 40.0, 31.8, 30.4, 29.5, 29.4, 29.3, 29.2, 28.9, 26.9, 22.7, 14.1; FTIR (neat) 3303, 3006, 2929, 2250, 1948, 1663, 1552, 1492, 1295, 827, 640 cm^{-1}; MS (ESI) m/z 352 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{22}H_{30}ON_3$ $(M + H)^+$ 352.2383, found 352.2384.

General Procedure for the Synthesis of Arylated Cyanoacetic Acid Derivatives. To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar, were added the amide derivative (**1**, 0.4 mmol), iodoarene (**2**, 1.2 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), $Mn(OAc)_2$ (138 mg, 0.8 mmol), Na_2CO_3 (85 mg, 0.8 mmol), and *t*-AmOH (4 mL). The mixture was stirred for 30 h at 130 °C followed by cooling. The reaction mixture was diluted with EtOAc (10 mL), filtered through a pad of Celite, and concentrated under reduced pressure. Water (10 mL) was added to the crude residue and the product extracted with EtOAc (10 mL × 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent, hexane/EtOAc = 10:1 to 6:1) to afford the desired arylated product (**3a–3s**, **4a–4f**, and **5a–5j**).

*2-Cyano-2-(4-methoxybenzyl)-N-(quinolin-8-yl)dodecanamide (**3a**).* Yield of 160 mg, 85%, as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.72 (dd, J = 5.9, 3.0 Hz, 1H), 8.12 (dd, J = 8.3, 1.7 Hz, 1H), 7.56–7.50 (m, 2H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 3.66 (s, 3H), 3.36 (d, J = 13.5 Hz, 1H), 3.06 (d, J = 13.5 Hz, 1H), 2.20 (td, J = 13.1, 4.4 Hz, 1H), 1.85 (td, J = 12.3, 4.2 Hz, 1H), 1.70–1.59 (m, 1H), 1.51–1.38 (m, 1H), 1.37–1.17 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.7, 159.1, 148.8, 138.7, 136.0, 133.5, 131.0, 127.8, 127.1, 126.7, 122.7, 121.8, 120.5, 116.6, 113.9, 55.1, 53.2, 42.7, 37.4, 31.9, 29.6, 29.5, 29.5, 29.4, 29.3, 25.6, 22.7, 14.4; FTIR (neat) 3306, 2924, 2853, 2232, 1686, 1612, 1529, 1325, 1178, 1034, 909, 790 cm^{-1}; MS (ESI) m/z 472 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{30}H_{38}O_2N_3$ $(M + H)^+$ 472.2959, found 472.2959.

*2-Cyano-N-(quinolin-8-yl)-2-(3,4,5-trimethoxybenzyl)-dodecanamide (**3b**).* Yield of 178 mg, 84%, as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.77 (dd, J = 4.2, 1.6 Hz, 1H), 8.71 (dd, J = 6.9, 1.9 Hz, 1H), 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.56–7.48 (m, 2H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 6.53 (s, 2H), 3.67 (s, 6H), 3.56 (s, 3H), 3.31 (d, J = 13.4 Hz, 1H), 3.05 (d, J = 13.4 Hz, 1H), 2.25 (td, J = 12.9, 4.4 Hz, 1H), 1.89 (td, J = 12.3, 4.2 Hz, 1H), 1.75–1.63 (m, 1H), 1.55–1.43 (m, 1H), 1.41–1.20 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.5, 152.9, 148.8, 138.6, 137.2, 136.0, 133.4, 130.2, 127.8, 126.8, 122.7, 121.9, 120.5, 116.4, 106.7, 60.5, 55.9, 53.2, 44.2, 37.4, 31.9, 29.5, 29.4, 29.4, 29.3, 29.2, 25.6, 22.6, 14.1; FTIR (neat) 3302, 2960, 2924, 2853, 2232, 1686, 1590, 1529, 1422, 1326, 1240, 1123, 1007, 826, 791 cm^{-1}; MS (ESI) m/z 532 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{32}H_{42}O_4N_3$ $(M + H)^+$ 532.3170, found 532.3172.

*2-Benzyl-2-cyano-N-(quinolin-8-yl)dodecanamide (**3c**).* Yield of 128 mg, 73%, as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.72 (dd, J = 6.1, 2.8 Hz, 1H), 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.56–7.50 (m, 2H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 7.36–7.32 (m, 2H), 7.25–7.20 (m, 2H), 7.19–7.14 (m, 1H), 3.42 (d, J = 13.4 Hz, 1H), 3.11 (d, J = 13.4 Hz, 1H), 2.21 (td, J = 13.1, 4.1 Hz, 1H), 1.86 (td, J = 12.3, 4.2 Hz, 1H), 1.71–1.58 (m, 1H), 1.51–1.40 (m, 1H), 1.37–1.17 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.5, 148.8, 138.7, 136.0, 134.6, 133.4, 130.0, 128.5, 127.7, 127.5, 126.9, 122.6, 121.8, 120.3, 116.6, 52.9, 43.4, 37.5, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 25.6, 22.6, 14.1; FTIR (neat) 3303, 3030, 2924, 2853, 2235, 1686, 1529, 1485, 1326, 1206, 1170, 910, 825, 699 cm^{-1}; MS (ESI) m/z 442 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{29}H_{36}ON_3$ $(M + H)^+$ 442.2855, found 442.2854.

*Methyl 4-(2-Cyano-2-(quinolin-8-ylcarbamoyl)dodecyl)benzoate (**3d**).* Yield of 125 mg, 63%, as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.76 (dd, J = 4.2, 1.6 Hz, 1H), 8.70 (dd, J = 6.8, 2.1 Hz, 1H), 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.58–7.50 (m, 2H), 7.44–7.39 (m, 3H), 3.82 (s, 3H), 3.48 (d, J = 13.3 Hz, 1H), 3.14 (d, J = 13.3 Hz, 1H), 2.24 (td, J = 13.0, 4.5 Hz, 1H), 1.88 (td, J = 12.3, 4.2 Hz, 1H), 1.70–1.58 (m, 1H), 1.53–1.40 (m, 1H), 1.37–1.18 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 165.0, 148.8, 139.8, 138.9, 136.0, 133.2, 130.0, 129.8, 129.4, 127.8, 126.9, 122.8, 121.8, 120.0, 116.7, 52.6, 52.0, 43.2, 37.7, 31.8, 29.5, 29.4, 29.3, 29.2, 29.2, 25.6, 22.7, 14.1; FTIR (neat) 3304, 2924, 2854, 2234, 1721, 1687, 1529, 1486, 1325, 1276, 1106, 1021, 791, 637 cm^{-1}; MS (ESI) m/z 500 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{31}H_{38}O_3N_3$ $(M + H)^+$ 500.2908, found 500.2908.

*2-(4-Acetylbenzyl)-2-cyano-N-(quinolin-8-yl)dodecanamide (**3e**).* Yield of 119 mg, 62%, as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.63 (s, 1H), 8.76 (dd, J = 4.2, 1.6 Hz, 1H), 8.70 (dd, J = 6.8, 2.2 Hz, 1H), 8.13 (dd, J = 8.3, 1.6 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.58–7.51 (m, 2H), 7.46–7.40 (m, 3H), 3.48 (d, J = 13.3 Hz, 1H), 3.15 (d, J = 13.3 Hz, 1H), 2.47 (s, 3H), 2.26 (td, J = 13.0, 4.4 Hz, 1H), 1.89 (td, J = 12.3, 4.2 Hz, 1H), 1.71–1.61 (m, 1H), 1.52–1.41 (m, 1H), 1.38–1.17 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.7, 165.0, 148.8, 140.1, 138.6, 136.3, 136.1, 133.2, 132.5, 130.2, 128.7, 128.5, 127.8, 126.9, 122.8, 121.9, 120.0, 116.7, 52.6, 43.1, 37.8, 31.8, 29.5, 29.5, 29.4, 29.3, 29.2, 26.5, 25.6, 22.6, 14.1; FTIR (neat) 3303, 2954, 2924, 2853, 2234, 1682, 1529, 1486, 1325, 1263, 1018, 826, 611 cm^{-1}; MS (ESI) m/z 484 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{31}H_{38}O_2N_3$ $(M + H)^+$ 484.2959, found 484.2954.

*2-Cyano-2-(4-cyanobenzyl)-N-(quinolin-8-yl)dodecanamide (**3f**).* Yield of 102 mg, 55%, as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.67 (dd, J = 7.3, 1.6 Hz, 1H), 8.15 (dd, J = 8.3, 1.6 Hz, 1H), 7.65–7.39 (m, 7H), 3.48 (d, J = 13.3 Hz, 1H), 3.13 (d, J = 13.3 Hz, 1H), 2.25 (td, J = 13.0, 4.4 Hz, 1H), 1.90 (td, J = 12.3, 4.2 Hz, 1H), 1.74–1.61 (m, 1H), 1.53–1.41 (m, 1H), 1.39–1.17 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.7, 148.9, 140.1, 138.6, 136.1,

DOI: 10.1021/acs.joc.5b02138
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133.0, 132.2, 131.1, 127.8, 126.9, 123.0, 122.0, 119.8, 118.5, 116.7, 111.6, 52.6, 43.1, 37.8, 31.8, 29.5, 29.4, 29.3, 29.2, 29.2, 25.5, 22.6, 14.1; FTIR (neat) 3303, 2924, 2853, 2229, 1686, 1529, 1485, 1425, 1326, 1170, 910, 825, 790, 608 cm^{-1}; MS (ESI) m/z 467 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{30}H_{35}ON_4$ $(M + H)^+$ 467.2805, found 467.2791.

2-Cyano-2-(4-nitrobenzyl)-N-(quinolin-8-yl)dodecanamide (**3g**). Yield of 140 mg, 72%, as a pale yellow solid; mp 140−141 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.75 (dd, J = 4.2, 1.6 Hz, 1H), 8.67 (dd, J = 7.2, 1.6 Hz, 1H), 8.14 (dd, J = 8.3, 1.6 Hz, 1H), 8.06 (d, J = 8.7 Hz, 2H), 7.59−7.53 (m, 2H), 7.51 (d, J = 8.7 Hz, 2H), 7.43 (dd, J = 8.3, 4.2 Hz, 1H), 3.53 (d, J = 13.3 Hz, 1H), 3.18 (d, J = 13.3 Hz, 1H), 2.26 (td, J = 13.1, 4.4 Hz, 1H), 1.92 (td, J = 12.3, 4.3 Hz, 1H), 1.74−1.64 (m, 1H), 1.54−1.42 (m, 1H), 1.39−1.18 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.6, 148.9, 147.4, 142.1, 138.6, 136.1, 133.0, 130.9, 127.8, 126.9, 123.7, 123.0, 122.0, 119.8, 116.7, 52.6, 42.8, 37.9, 31.8, 29.5, 29.4, 29.3, 29.2, 29.2, 25.6, 22.6, 14.1; FTIR (neat) 3320, 2924, 2853, 2236, 1690, 1530, 1487, 1425, 1299, 1007, 827, 792, 757 cm^{-1}; MS (ESI) m/z 487 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{29}H_{35}O_3N_4$ $(M + H)^+$ 487.2704, found 487.2707.

2-Cyano-2-(2-methoxybenzyl)-N-(quinolin-8-yl)dodecanamide (**3h**). Yield of 84 mg, 45%, as a brown oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.79−8.73 (m, 2H), 8.13 (dd, J = 8.3, 1.6 Hz, 1H), 7.56−7.51 (m, 2H), 7.43 (dd, J = 8.3, 4.2 Hz, 1H), 7.28−7.25 (m, 1H), 7.15 (td, J = 15.6, 1.7 Hz, 1H), 6.82 (td, J = 7.4, 1.0 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 3.69 (s, 3H), 3.35 (dd, J = 14.9, 13.6 Hz, 2H), 2.25 (td, J = 12.5, 4.4 Hz, 1H), 1.86 (td, J = 12.2, 4.2 Hz, 1H), 1.70−1.59 (m, 1H), 1.51−1.40 (m, 1H), 1.37−1.18 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 157.9, 148.7, 138.7, 136.0, 133.7, 131.6, 129.0, 127.7, 127.0, 123.3, 122.4, 121.8, 120.4, 120.3, 116.5, 110.4, 55.1, 52.2, 37.2, 37.0, 31.8, 29.7, 29.5, 29.4, 29.3, 29.2, 25.6, 22.6, 14.4; FTIR (neat) 3305, 2923, 2855, 2233, 1687, 1529, 1425, 1291, 1157, 825, 757 cm^{-1}; MS (ESI) m/z 472 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{30}H_{38}O_2N_3$ $(M + H)^+$ 472.2959, found 472.2959.

2-Cyano-2-(2,4-dimethoxybenzyl)-N-(quinolin-8-yl)-dodecanamide (**3i**). Yield of 112 mg, 56%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.79−8.73 (m, 2H), 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.57−7.50 (m, 2H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.34 (dd, J = 8.3, 2.4 Hz, 1H), 6.29 (d, J = 2.4 Hz, 1H), 3.68 (s, 3H). 3.64 (s, 3H), 3.28 (dd, J = 17.6, 13.6 Hz, 2H), 2.24 (td, J = 13.1, 4.4 Hz, 1H), 1.84 (td, J = 12.3, 4.2 Hz, 1H), 1.70−1.58 (m, 1H), 1.50−1.39 (m, 1H), 1.37−1.18 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 160.4, 158.8, 148.6, 138.7, 136.0, 133.7, 132.0, 127.8, 127.0, 122.4, 121.7, 120.6, 116.5, 115.7, 104.1, 98.3, 55.2, 55.1, 52.5, 37.1, 36.7, 31.8, 29.5, 29.5, 29.4, 29.3, 29.2, 25.7, 22.7, 14.1; FTIR (neat) 3308, 2924, 2853, 2233, 1687, 1528, 1424, 1290, 1208, 1157, 1035, 825, 790, 756 cm^{-1}; MS (ESI) m/z 502 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{31}H_{40}O_3N_3$ $(M + H)^+$ 502.3064, found 502.3066.

2-(4-Chlorobenzyl)-2-cyano-N-(quinolin-8-yl)dodecanamide (**3j**). Yield of 140 mg, 74%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.79 (dd, J = 4.2, 1.6 Hz, 1H), 8.69 (dd, J = 6.9, 1.9 Hz, 1H), 8.13 (dd, J = 8.3, 1.6 Hz, 1H), 7.58−7.50 (m, 2H), 7.43 (dd, J = 8.3, 4.2 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 3.39 (d, J = 13.5 Hz, 1H), 3.06 (d, J = 13.5 Hz, 1H), 2.21 (td, J = 12.9, 4.4 Hz, 1H), 1.86 (td, J = 12.9, 4.4 Hz, 1H), 1.73−1.59 (m, 1H), 1.52−1.39 (m, 1H), 1.37−1.16 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.2, 148.8, 148.6, 138.6, 136.0, 133.6, 133.2, 133.1, 131.3, 128.6, 127.8, 126.9, 122.8, 121.9, 120.1, 116.6, 52.8, 42.6, 37.6, 31.8, 29.5, 29.4, 29.4, 29.3, 29.2, 25.6, 22.6, 14.1; FTIR (neat) 2924, 2853, 2233, 1686, 1529, 1486, 1326, 1092, 910, 806, 790 cm^{-1}; MS (ESI) m/z 476 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{29}H_{35}ClON_3$ $(M + H)^+$ 476.2463, found 476.2466.

2-Cyano-2-(3-fluoro-5-nitrobenzyl)-N-(quinolin-8-yl)-dodecanamide (**3k**). Yield of 143 mg, 71%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.66 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.68 (dd, J = 7.1, 1.8 Hz, 1H), 8.15 (dd, J = 8.3, 1.6 Hz, 1H), 8.03 (s, 1H), 7.72 (dt, J = 8.2, 2.2 Hz, 1H), 7.60−7.52 (m, 2H), 7.47−7.42 (m, 2H), 3.55 (d, J = 13.5 Hz, 1H), 3.16 (d, J = 13.5 Hz, 1H), 2.26 (td, J = 13.0, 4.5 Hz, 1H), 1.90 (td, J = 12.3, 4.2 Hz, 1H), 1.75−1.66 (m, 1H), 1.55−1.43 (m, 1H), 1.40−1.17 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.4, 163.3, 160.8, 148.9, 138.7, 136.2, 132.8,127.8, 127.1, 123.5, 123.1, 121.9, 120.9, 119.5, 116.9, 110.8, 110.5, 52.4, 42.4, 37.8, 31.8, 29.7, 29.4, 29.4, 29.2, 29.2, 25.5, 22.6, 14.1; FTIR (neat) 3299, 2924, 2854, 2235, 1687, 1529, 1485, 1352, 1147, 882, 790 cm^{-1}; MS (ESI) m/z 505 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{29}H_{34}FO_3N_4$ $(M + H)^+$ 505.2609, found 505.2610.

Methyl 3-Bromo-5-(2-cyano-2-(quinolin-8-ylcarbamoyl)dodecyl)-benzoate (**3l**). Yield of 150 mg, 65%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.77 (dd, J = 4.2, 1.6 Hz, 1H), 8.69 (dd, J = 6.6, 2.3 Hz, 1H), 8.14 (dd, J = 8.3, 1.6 Hz, 1H), 7.92 (dt, J = 12.0, 3.3 Hz, 1H), 7.66 (t, J = 1.6 Hz, 1H), 7.59−7.51 (m, 2H), 7.44 (dd, J = 8.3, 4.2 Hz, 1H), 3.78 (s, 3H), 3.42 (d, J = 13.4 Hz, 1H), 3.10 (d, J = 13.4 Hz, 1H), 2.24 (td, J = 13.4, 4.5 Hz, 1H), 1.87 (td, J = 12.8, 4.2 Hz, 1H), 1.73−1.61 (m, 1H), 1.54−1.41 (m. 1H), 1.40−1.19 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.3, 164.9, 148.8, 138.6, 137.7, 137.0, 136.0, 133.0, 132.0, 131.9, 129.7. 126.9, 122.9, 122.5, 121.9, 119.7, 116.9, 52.6, 52.3, 42.7, 37.4, 31.8, 29.5, 29.4, 29.3, 29.2, 25.6, 22.6, 14.1; FTIR (neat) 2924, 2853, 1726, 1686, 1528, 1485, 1425, 1280, 1204, 886, 825, 763 cm^{-1}; MS (ESI) m/z 578 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{31}H_{37}BrO_3N_3$ $(M + H)^+$ 578.2013, found 578.2014.

2-((5-Acetylthiophen-2-yl)methyl)-2-cyano-N-(quinolin-8-yl)-dodecanamide (**3m**). Yield of 121 mg, 62%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.81 (s, 1H), 8.85 (dd, J = 4.2, 1.6 Hz, 1H), 8.74 (dd, J = 7.1, 1.8 Hz, 1H), 8.19 (dd, J = 8.3, 1.6 Hz, 1H), 7.63−7.55 (m, 1H), 7.52−7.46 (m, 2H), 7.10 (d, J = 3.8 Hz, 1H), 3.70 (d, J = 14.5 Hz, 3H), 3.35 (d, J = 14.5 Hz, 1H), 2.44 (s, 3H), 2.21 (td, J = 13.4, 4.4 Hz, 1H), 1.95 (td, J = 12.3, 4.3 Hz, 1H), 1.75−1.65 (m, 1H), 1.55−1.42 (m. 1H), 1.41−1.18 (m, 14H), 0.87 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.7, 148.9, 145.2, 144.1, 138.7, 136.1, 133.2, 132.6, 129.1, 127.8, 127.0, 122.9, 121.9, 119.8, 116.9, 52.7, 37.7, 37.7, 31.8, 29.5, 29.4, 29.4, 29.3, 29.2, 29.1, 26.6, 25.5, 22.6, 14.1; FTIR (neat) 2955, 2924, 2853, 2235, 1686, 1660, 1528, 1485, 1326, 1273, 928, 825, 790 cm^{-1}; MS (ESI) m/z 490 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{29}H_{36}N_3O_2S$ $(M + H)^+$ 490.2523, found 490.2525.

2-((1-Benzyl-1H-pyrazol-4-yl)methyl)-2-cyano-N-(quinolin-8-yl)-dodecanamide (**3n**). Yield of 158 mg, 76%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.83 (dd, J = 4.2, 1.6 Hz, 1H), 8.69 (dd, J = 7.4, 1.5 Hz, 1H), 8.16 (dd, J = 8.3, 1.6 Hz, 1H), 7.59−7.49 (m, 3H), 7.46 (dd, J = 8.3, 4.2 Hz, 1H), 7.37 (s, 1H), 7.14−7.09 (m, 1H), 7.07−7.01 (m, 2H), 6.99−6.96 (m, 2H), 5.14 (s, 2H), 3.28 (d, J = 14.3 Hz, 1H), 2.99 (d, J = 14.3 Hz, 1H), 2.16 (td, J = 13.1, 4.4 Hz, 1H), 1.87 (td, J = 12.2, 4.2 Hz, 1H), 1.70−1.59 (m, 1H), 1.51−1.38 (m, 1H), 1.36−1.16 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 148.8, 140.3, 138.7, 136.3, 136.1, 133.3, 129.3, 128.5, 127.8, 127.7, 127.3, 127.0, 122.7, 121.9, 120.7, 116.6, 114.6, 55.9, 53.1, 37.3, 33.0, 31.8, 29.5, 29.4, 29.3, 29.2, 29.2, 25.6, 22.6, 14.1; FTIR (neat) 3304, 2923, 2853, 2232, 1684, 1529, 1485, 1455, 1326, 1170, 909, 825, 790, 696 cm^{-1}; MS (ESI) m/z 522 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{33}H_{40}ON_5$ $(M + H)^+$ 522.3227, found 522.3226.

2-Cyano-2-(pyridin-2-ylmethyl)-N-(quinolin-8-yl)dodecanamide (**3o**). Yield of 106 mg, 60%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.85 (s, 1H), 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.73 (dd, J = 6.7, 2.2 Hz, 1H), 8.45 (d, J = 4.2 Hz, 1H), 8.15 (dd, J = 8.3, 1.6 Hz, 1H), 7.58−7.51 (m, 3H), 7.45 (dd, J = 8.3, 4.2 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.07 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H), 3.66 (d, J = 14.2 Hz, 1H), 3.33 (d, J = 14.2 Hz, 1H), 2.26 (td, J = 13.3, 4.6 Hz, 1H), 1.96 (td, J = 12.5, 4.3 Hz, 1H), 1.77−1.63 (m, 1H), 1.57−1.44 (m, 1H), 1.39−1.17 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 155.3, 149.4, 148.8, 138.8, 136.4, 136.0, 133.7, 127.8, 127.0, 123.8, 122.5, 122.2, 121.8, 120.3, 116.7, 51.0, 44.7, 37.9, 31.8, 29.5, 29.4, 29.4, 29.3, 29.2, 25.4, 22.6, 14.1; FTIR (neat) 3292, 2948, 2920, 2851, 2240, 1678, 1589, 1529, 1426, 1325, 1256, 910, 834,

DOI: 10.1021/acs.joc.5b02138
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778 cm^{-1}; MS (ESI) m/z 443 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{28}H_{35}ON_4$ $(M + H)^+$ 443.2805, found 443.2806.

*2-Cyano-2-((6-methoxypyrazin-2-yl)methyl)-N-(quinolin-8-yl)-dodecanamide (**3p**).* Yield of 117 mg, 62%, as a brown solid; mp 60−61 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.90 (s, 1H), 8.85 (dd, J = 4.2, 1.6 Hz, 1H), 8.69 (dd, J = 7.3, 1.6 Hz, 1H), 8.17 (dd, J = 8.3, 1.6 Hz, 1H), 8.05 (s, 1H), 7.99 (s, 1H), 7.59−7.50 (m, 2H), 7.48 (dd, J = 8.3, 4.2 Hz, 1H), 3.66 (s, 3H), 3.65 (d, J = 15.1 Hz, 1H), 3.26 (d, J = 15.1 Hz, 1H), 2.23 (td, J = 13.1, 4.1 Hz, 1H), 1.99 (td, J = 12.6, 4.2 Hz, 1H), 1.88−1.68 (m, 1H), 1.59−1.46 (m, 1H), 1.41−1.19 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 159.7, 148.8, 147.4, 138.6, 136.2, 135.6, 134.1, 133.5, 127.8, 127.1, 122.6, 121.9, 120.3, 116.6, 53.7, 49.6, 40.7, 38.5, 31.8, 29.5, 29.4, 29.3, 29.2, 29.2, 25.3, 22.6, 14.1; FTIR (neat) 3299, 2924, 2854, 2236, 1686, 1541, 1485, 1302, 1245, 1009, 905, 799, 665 cm^{-1}; MS (ESI) m/z 474 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{28}H_{36}O_2N_5$ $(M + H)^+$ 474.2864, found 474.2864.

*2-((6-Chloropyridin-3-yl)methyl)-2-cyano-N-(quinolin-8-yl)-dodecanamide (**3q**).* Yield of 143 mg, 75%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.80 (dd, J = 4.2, 1.6 Hz, 1H), 8.68 (dd, J = 7.3, 1.5 Hz, 1H), 8.35 (d, J = 2.2 Hz, 1H), 8.15 (dd, J = 8.3, 1.6 Hz, 1H), 7.65 (dd, J = 8.2, 2.5 Hz, 1H), 7.60−7.50 (m, 2H), 7.45 (dd, J = 8.3, 4.2 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 3.44 (d, J = 13.7 Hz, 1H), 3.07 (d, J = 13.7 Hz, 1H), 2.23 (td, J = 12.9, 4.5 Hz, 1H), 1.91 (td, J = 12.9, 4.4 Hz, 1H), 1.75−1.61 (m, 1H), 1.53−1.41 (m, 1H), 1.40−1.18 (m, 14H), 0.86 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.6, 151.0, 150.8, 148.9, 140.2, 138.6, 136.2, 129.4, 127.8, 126.9, 124.7, 123.2, 121.9, 119.7, 116.8, 52.5, 39.6, 37.8, 31.9, 29.5, 29.4, 29.4, 29.3, 29.2, 25.6, 22.6, 14.1; FTIR (neat) 2924, 2853, 2232, 1686, 1529, 1460, 1386, 1105, 825, 790 cm^{-1}; MS (ESI) m/z 477 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{28}H_{34}ClON_4$ $(M + H)^+$ 477.2416, found 477.2416.

*2-((1H-Indol-5-yl)methyl)-2-cyano-N-(quinolin-8-yl)-dodecanamide (**3r**).* Yield of 155 mg, 81%, as a brown semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.73 (dd, J = 6.7, 2.2 Hz, 1H), 8.60 (dd, J = 4.2, 1.6 Hz, 1H), 8.15 (s, 1H), 8.01 (dd, J = 8.3, 1.6 Hz, 1H), 7.60 (s, 1H), 7.51−7.44 (m, 2H), 7.29 (dd, J = 8.3, 4.2 Hz, 1H), 7.18−7.11 (m, 2H), 7.04 (t, J = 2.9 Hz, 1H), 6.39 (t, J = 4.5 Hz, 1H), 3.52 (d, J = 13.6 Hz, 1H), 3.21 (d, J = 13.6 Hz, 1H), 2.23 (td, J = 13.1, 4.5 Hz, 1H), 1.84 (td, J = 12.5, 4.2 Hz, 1H), 1.69−1.58 (m, 1H), 1.51−1.39 (m, 1H), 1.35−1.16 (m, 14H), 0.84 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 148.7, 138.7, 136.0, 135.3, 133.5, 128.0, 127.8, 127.0, 125.8, 124.6, 124.0, 122.6, 122.2, 121.7, 120.8, 116.7, 111.0, 102.5, 53.6, 43.8, 37.4, 31.9, 29.7, 29.5, 29.4, 29.3, 29.3, 25.7, 22.7, 14.2; FTIR (neat) 3379, 3304, 2923, 2853, 2233, 1686, 1528, 1485, 1326, 1965, 908, 825, 729 cm^{-1}; MS (ESI) m/z 481 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{31}H_{37}ON_4$ $(M + H)^+$ 481.2962, found 481.2964.

*2-Cyano-2-((2,3-dihydrobenzofuran-5-yl)methyl)-N-(quinolin-8-yl)dodecanamide (**3s**).* Yield of 156 mg, 81%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.70 (dd, J = 6.1, 2.8 Hz, 1H), 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.56−7.50 (m, 2H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 7.12 (s, 1H), 7.07 (dd, J = 8.2, 1.8 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 4.45−4.37 (m, 1H), 4.36−4.28 (m, 1H), 3.32 (d, J = 13.6 Hz, 1H), 3.12−3.03 (m, 1H), 3.02 (d, J = 13.6 Hz, 1H), 2.90−2.80 (m, 1H), 2.20 (td, J = 13.1, 4.4 Hz, 1H), 1.85 (td, J = 12.2, 4.2 Hz, 1H), 1.71−1.59 (m, 1H), 1.52−1.40 (m, 1H), 1.37−1.15 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 159.5, 148.7, 138.6, 136.0, 133.5, 129.7, 127.8, 127.1, 126.9, 126.5, 122.6, 121.8, 120.5, 116.6, 109.1, 71.1, 53.3, 43.2, 37.2, 31.8, 29.7, 29.5, 29.4, 29.4, 29.3, 29.2, 29.2, 25.6, 22.7, 14.1; FTIR (neat) 3306, 2923, 2853, 2233, 1686, 1528, 1487, 1325, 1243, 1105, 982, 825, 790, 693 cm^{-1}; MS (ESI) m/z 484 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{31}H_{38}O_2N_3$ $(M + H)^+$ 484.2959, found 484.2954.

*2-Benzyl-2-cyano-3-(4-methoxyphenyl)-N-(quinolin-8-yl)-propanamide (**4a**).* Yield of 149 mg, 89%, as a brown solid; mp 117−118 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.70−8.66 (m, 2H), 8.08 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 4.2 Hz, 2H), 7.40−7.33 (m, 3H), 7.30−7.12 (m, 5H), 6.74 (d, J = 8.5 Hz, 2H), 3.66 (s, 3H), 3.51 (dd, J = 16.5, 13.1 Hz, 2H), 3.12 (dd, J = 15.7, 13.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.9, 159.0, 148.6, 138.6, 135.9, 134.5, 133.3, 131.2, 130.0, 128.5, 127.6, 127.6, 126.9, 126.5, 122.6, 121.7, 119.8, 116.6, 113.9, 55.0, 54.7, 42.9, 42.4; FTIR (neat) 3304, 3030, 2942, 2830, 2233, 1686, 1530, 1426, 1325, 1179, 1035, 790 cm^{-1}; MS (ESI) m/z 422 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{27}H_{24}O_2N_3$ $(M + H)^+$ 422.1863, found 422.1863.

*2-Benzyl-2-cyano-N-(quinolin-8-yl)-3-(3,4,5-trimethoxyphenyl)-propanamide (**4b**).* Yield of 159 mg, 83%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.69 (dd, J = 5.6, 3.3 Hz, 1H), 8.66 (dd, J = 4.2, 1.6 Hz, 1H), 8.06 (dd, J = 8.3, 1.6 Hz, 1H), 7.52−7.47 (m, 2H), 7.40 (d, J = 7.0 Hz, 2H), 7.36 (dd, J = 8.3, 4.2 Hz, 1H), 7.30−7.19 (m, 3H), 6.53 (s, 2H), 3.66 (s, 6H), 3.58 (d, J = 13.4 Hz, 1H), 3.53 (s, 3H), 3.43 (d, J = 13.4 Hz, 1H), 3.18 (d, J = 13.5 Hz, 1H), 3.08 (d, J = 13.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.9, 152.9, 148.7, 138.5, 137.2, 135.9, 134.5, 133.3, 130.2, 129.9, 128.6, 127.7, 127.6, 126.7, 122.7, 121.8, 119.8, 116.3, 106.7, 60.5, 55.9, 54.5, 43.8, 42.8; FTIR (neat) 2936, 2837, 2248, 1683, 1590, 1528, 1485, 1326, 1240, 1124, 1004, 826, 698 cm^{-1}; MS (ESI) m/z 482 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{29}H_{28}O_4N_3$ $(M + H)^+$ 482.2074, found 482.2076.

*2-Benzyl-2-cyano-3-phenyl-N-(quinolin-8-yl)propanamide (**4c**).* Yield of 116 mg, 74%, as a brown solid; mp 129−130 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.69 (dd, J = 5.4, 3.3 Hz, 1H), 8.64 (d, J = 2.9 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.55−7.49 (m, 2H), 7.40−7.32 (m, 5H), 7.27−7.12 (m, 6H), 3.55 (d, J = 13.4 Hz, 2H), 3.15 (d, J = 13.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.8, 148.6, 138.5, 135.8, 134.4, 133.2, 130.1, 128.5, 127.6, 127.5, 126.8, 122.6, 121.7, 119.7, 116.5, 54.4, 43.0; FTIR (neat) 3274, 3063, 2933, 2235, 1679, 1530, 1514, 1455, 1327, 1249, 1091, 1030, 910, 823, 758 cm^{-1}; MS (ESI) m/z 392 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{26}H_{22}ON_3$ $(M + H)^+$ 392.1757, found 392.1755.

*Methyl 4-(2-Benzyl-2-cyano-3-oxo-3-(quinolin-8-ylamino)-propyl)benzoate (**4d**).* Yield of 115 mg, 64%, as a white solid; mp 191−192 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.67 (t, J = 4.5 Hz, 1H), 8.62 (dd, J = 4.2, 1.6 Hz, 1H), 8.06 (dd, J = 8.3, 1.6 Hz, 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 4.2 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.39−7.31 (m, 3H), 7.26−7.21 (m, 2H), 7.20−7.15 (m, 1H), 3.81 (s, 3H), 3.51 (dd, J = 15.0, 13.4 Hz, 2H), 3.17 (dd, J = 13.3, 7.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.7, 164.4, 148.6, 139.7, 138.5, 135.9, 134.1, 133.0, 130.1, 130.1, 129.8, 129.4, 128.6, 127.8, 127.6, 126.8, 122.8, 121.7, 119.4, 116.6, 54.1, 52.0, 43.3, 42.7; FTIR (neat) 3340, 3048, 3009, 2941, 2233, 1690, 1712, 1524, 1487, 1289, 1172, 1111, 983, 823, 738 cm^{-1}; MS (ESI) m/z 450 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{28}H_{24}O_3N_3$ $(M + H)^+$ 450.1812, found 450.1814.

*2-(4-Acetylbenzyl)-2-cyano-3-phenyl-N-(quinolin-8-yl)-propanamide (**4e**).* Yield of 121 mg, 70%, as a white solid; mp 172−173 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.67 (dd, J = 5.1, 3.8 Hz, 1H), 8.60 (dd, J = 4.2, 1.6 Hz, 1H), 8.05 (dd, J = 8.3, 1.6 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.54−7.48 (m, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 7.0 Hz, 2H), 7.33 (dd, J = 8.2, 4.2 Hz, 1H), 7.26−7.21 (m, 2H), 7.20−7.15 (m, 1H), 3.59 (dd, J = 14.6, 13.4 Hz, 2H), 3.18 (dd, J = 13.2, 9.7 Hz, 2H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.6, 164.4, 148.6, 139.9, 138.5, 136.3, 135.9, 134.1, 133.0, 130.3, 130.1, 128.6, 128.5, 127.8, 127.6, 126.8, 122.8, 121.7, 119.4, 116.6, 54.1, 43.3, 42.7, 26.5; FTIR (neat) 3337, 3042, 2924, 2852, 223, 1691, 1675, 1523, 1486, 1269, 1172, 1089, 960, 822, 739, 632 cm^{-1}; MS (ESI) m/z 434 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{28}H_{24}O_2N_3$ $(M + H)^+$ 434.1863, found 434.1863.

*2-Benzyl-2-cyano-3-(4-cyanophenyl)-N-(quinolin-8-yl)-propanamide (**4f**).* Yield of 101 mg, 61%, as a white solid; mp 170−171 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.69−8.61 (m, 2H), 8.10 (dd, J = 8.3, 1.5 Hz, 1H), 7.55−7.51 (m, 2H), 7.50−7.43 (m, 4H), 7.42−7.35 (m, 3H), 7.29−7.17 (m, 3H), 3.59 (dd, J = 13.2, 10.9 Hz, 2H), 3.21 (d, J = 13.4 Hz, 1H), 3.13 (d, J = 13.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.1, 148.7, 140.0, 138.5, 136.0, 133.9, 132.9, 132.3, 130.9, 130.1, 128.7, 128.0, 127.7, 126.8, 123.0, 121.9, 119.3, 118.5, 116.6, 111.7, 54.1, 43.4, 42.7; FTIR (neat) 3274, 3060, 2225, 1679, 1526, 1486, 1328, 1208, 1174, 1019, 915, 824, 699

DOI: 10.1021/acs.joc.5b02138
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cm^{-1}; MS (ESI) m/z 417 (M + H)$^+$; HRMS (ESI) m/z calcd for $C_{27}H_{21}ON_4$ (M + H)$^+$ 417.1710, found 417.1712.

*2-Cyano-2-(4-methoxybenzyl)-N-(quinolin-8-yl)heptanamide (**5a**).* Yield of 123 mg, 77%, as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.63 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.72 (dd, J = 5.9, 3.0 Hz, 1H), 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.56−7.50 (m, 2H), 7.41 (dd, J = 8.3, 4.2 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 3.66 (s, 3H), 3.36 (d, J = 13.5 Hz, 1H), 3.06 (d, J = 13.5 Hz, 1H), 2.20 (td, J = 13.6, 4.8 Hz, 1H), 1.85 (td, J = 12.2, 4.3 Hz, 1H), 1.70−1.59 (m, 1H), 1.51−1.39 (m, 1H), 1.37−1.26 (m, 4H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.6, 158.9, 148.7, 138.7, 136.0, 133.4, 131.0, 127.6, 126.9, 126.6, 122.6, 121.8, 120.4, 116.6, 113.8, 55.0, 53.2, 42.7, 37.3, 31.5, 25.3, 22.3, 13.9; FTIR (neat) 3306, 2928, 2859, 2233, 1685, 1528, 1485, 1325, 1247, 1178, 1033, 909, 825, 790 cm^{-1}; MS (ESI) m/z 402 (M + H)$^+$; HRMS (ESI) m/z calcd for $C_{25}H_{28}O_2N_3$ (M + H)$^+$ 402.2176, found 402.2176.

*2-Cyano-2-(4-methoxybenzyl)-N-(quinolin-8-yl)octadecanamide (**5b**).* Yield of 184 mg, 83%, as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.63 (s, 1H), 8.77 (dd, J = 4.2, 1.6 Hz, 1H), 8.75 (dd, J = 5.2, 3.7 Hz, 1H), 8.10 (dd, J = 8.2, 1.6 Hz, 1H), 7.56−7.49 (m, 2H), 7.40 (dd, J = 8.3, 4.2 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 3.65 (s, 3H), 3.36 (d, J = 13.6 Hz, 1H), 3.05 (d, J = 13.6 Hz, 1H), 2.20 (td, J = 13.0, 4.4 Hz, 1H), 1.85 (td, J = 12.4, 4.2 Hz, 1H), 1.70−1.58 (m, 1H), 1.51−1.39 (m, 1H), 1.38−1.18 (m, 26H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.6, 159.0, 148.7, 138.7, 136.0, 133.4, 131.0, 127.7, 127.0, 126.7, 122.6, 121.8, 120.4, 116.6, 113.8, 55.0, 53.2, 42.7, 37.4, 31.9, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.5, 29.5, 29.4, 29.3, 29.3, 25.6, 22.7, 14.1; FTIR (neat) 3337, 2922, 2852, 2233, 1689, 1528, 1513, 1486, 1327, 1250, 1178, 960, 824, 757 cm^{-1}; MS (ESI) m/z 556 (M + H)$^+$; HRMS (ESI) m/z calcd for $C_{36}H_{50}O_2N_3$ (M + H)$^+$ 556.3898, found 556.3894.

*2-Cyano-3-cyclohexyl-2-(4-methoxybenzyl)-N-(quinolin-8-yl)-propanamide (**5c**).* Yield of 132 mg, 78%, as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.77 (dd, J = 4.2, 1.6 Hz, 1H), 8.68 (dd, J = 5.7, 3.2 Hz, 1H), 8.11 (dd, J = 8.2, 1.6 Hz, 1H), 7.57−7.49 (m, 2H), 7.41 (dd, J = 8.2, 4.2 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 6.70 (d, J = 8.7 Hz, 2H), 3.62 (s, 3H), 3.32 (d, J = 13.5 Hz, 1H), 3.02 (d, J = 13.5 Hz, 1H), 2.21 (td, J = 13.9, 7.2 Hz, 1H), 1.92 (d, J = 12.6 Hz, 1H), 1.82−1.55 (m, 7H), 1.27−0.93 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.9, 159.0, 148.7, 138.7, 136.0, 133.5, 131.1, 127.7, 127.0, 126.4, 122.6, 121.8, 120.6, 116.6, 113.8, 55.0, 51.7, 44.1, 43.9, 35.5, 34.0, 33.1, 26.0, 26.0, 25.9; FTIR (neat) 3305, 2923, 2850, 2233, 1686, 1612, 1527, 1512, 1463, 1326, 1249, 1178, 1033, 908, 825, 608 cm^{-1}; MS (ESI) m/z 428 (M + H)$^+$; HRMS (ESI) m/z calcd for $C_{27}H_{30}O_2N_3$ (M + H)$^+$ 428.2333, found 428.2332.

*2-Cyano-2-(4-methoxybenzyl)-4-phenyl-N-(quinolin-8-yl)-butanamide (**5d**).* Yield of 143 mg, 82%, as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 1H), 8.77 (dd, J = 4.2, 1.6 Hz, 1H), 8.72 (dd, J = 5.4, 3.5 Hz, 1H), 8.09 (dd, J = 8.3, 1.6 Hz, 1H), 7.55−7.49 (m, 2H), 7.40 (dd, J = 8.3, 4.2 Hz, 1H), 7.28−7.12 (m, 7H), 6.73 (d, J = 8.7 Hz, 2H), 3.64 (s, 3H), 3.39 (d, J = 13.6 Hz, 1H), 3.09 (dd, J = 13.6 Hz, 1H), 2.94 (td, J = 12.9, 4.6 Hz, 1H), 2.77 (td, J = 12.7, 4.9 Hz, 1H), 2.54 (td, J = 13.4, 5.0 Hz, 1H), 2.13 (td, J = 12.5, 4.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.2, 159.0, 148.7, 139.9, 138.7, 136.0, 133.3, 131.0, 128.5, 128.4, 127.7, 126.9, 126.4, 126.3, 122.7, 121.8, 120.2, 116.7, 113.9, 55.0, 52.9, 42.8, 39.0, 31.0; FTIR (neat) 3303, 3029, 2930, 2836, 2234, 1684, 1528, 1424, 1326, 1178, 908, 790, 697 cm^{-1}; MS (ESI) m/z 436 (M + H)$^+$; HRMS (ESI) m/z calcd for $C_{28}H_{26}O_2N_3$ (M + H)$^+$ 436.2020, found 436.2020.

*2-Cyano-2-(4-methoxybenzyl)-5-phenyl-N-(quinolin-8-yl)-pentanamide (**5e**).* Yield of 150 mg, 84%, as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.75 (dd, J = 4.2, 1.6 Hz, 1H), 8.70 (dd, J = 5.8, 1.2 Hz, 1H), 8.10 (dd, J = 8.3, 1.6 Hz, 1H), 7.55−7.49 (m, 2H), 7.40 (dd, J = 8.2, 4.2 Hz, 1H), 7.26−7.20 (m, 4H), 7.16−7.12 (m, 3H), 6.73 (d, J = 8.7 Hz, 2H), 3.65 (s, 3H), 3.55 (d, J = 13.6 Hz, 1H), 3.05 (dd, J = 13.6 Hz, 1H), 2.74−2.59 (m, 2H), 2.32−2.22 (m, 1H), 2.05−1.74 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.4, 159.0, 148.7, 141.0, 138.7, 136.0, 133.3, 131.0, 128.4, 128.3, 127.7, 126.9, 126.5, 126.0, 122.7, 121.8, 120.3, 116.7, 113.9, 55.0, 53.0, 42.7, 36.9, 35.4, 27.2; FTIR (neat) 3030, 2931, 2836, 2233, 1684, 1611, 1528, 1485, 1325, 1178, 1031, 908, 825, 698 cm^{-1}; MS (ESI) m/z 450 (M + H)$^+$; HRMS (ESI) m/z calcd for $C_{29}H_{28}O_2N_3$ (M + H)$^+$ 450.2176, found 450.2176.

*2-Cyano-3-(4-methoxyphenyl)-2-methyl-N-(quinolin-8-yl)-propanamide (**5f**).* **5f** was obtained according to the general procedure as a pale yellow solid (69 mg, 50%) along with the diarylated product **5g** (29%): mp 104−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (s, 1H), 8.79 (dd, J = 4.2, 1.6 Hz, 1H), 8.70 (dd, J = 6.3, 2.6 Hz, 1H), 8.14 (dd, J = 8.3, 1.6 Hz, 1H), 7.58−7.51 (m, 2H), 7.44 (dd, J = 8.3, 4.2 Hz, 1H), 7.29−7.24 (m, 2H), 6.77 (d, J = 8.3 Hz, 2H), 3.70 (s, 3H), 3.38 (d, J = 13.6 Hz, 1H), 3.06 (d, J = 13.6 Hz, 1H), 1.76 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.0, 159.0, 148.7, 138.7, 136.1, 133.4, 131.1, 127.7, 127.0, 126.6, 122.6, 121.8, 121.0, 116.7, 113.9, 55.1, 47.1, 43.3, 23.6; FTIR (neat) 3287, 2931, 2835, 2234, 1684, 1532, 1511, 1487, 1331, 1252, 1123, 1028, 806, 761 cm^{-1}; MS (ESI) m/z 346 (M + H)$^+$; HRMS (ESI) m/z calcd for $C_{21}H_{20}O_2N_3$ (M + H)$^+$ 346.1550, found 346.1550.

*2-Cyano-2-(4-methoxybenzyl)-3-(4-methoxyphenyl)-N-(quinolin-8-yl)propanamide (**5g**).* **5g** was obtained according to the general procedure as a pale yellow solid (155 mg, 86%) from **5f**, and 52 mg (29%) of **5g** was furnished from **1h**, along with monoarylated compound **5f**: mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.70−8.64 (m, 2H), 8.07 (dd, J = 8.2, 1.1 Hz, 1H), 7.51 (d, J = 3.8 Hz, 2H), 7.36 (dd, J = 8.2, 4.1 Hz, 1H), 7.26 (d, J = 8.7 Hz, 4H), 6.73 (d, J = 8.7 Hz, 4H), 3.66 (s, 6H), 3.47 (d, J = 13.5 Hz, 2H), 3.08 (d, J = 13.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.1, 159.0, 148.6, 138.6, 135.9, 133.3, 131.1, 127.6, 126.9, 126.5, 122.6, 121.7, 119.9, 116.5, 113.9, 55.0, 54.9, 42.2; FTIR (neat) 3301, 2932, 2835, 2235, 1683, 1611, 1529, 1511, 1424, 1326, 1245, 1177, 1030, 909, 825, 790 cm^{-1}; MS (ESI) m/z 452 (M + H)$^+$; HRMS (ESI) m/z calcd for $C_{28}H_{26}O_3N_3$ (M + H)$^+$ 452.1969, found 452.1971.

*2-Cyano-2-(4-methoxybenzyl)-5-methyl-N-(quinolin-8-yl)-hexanamide (**5h**).* Yield of 129 mg, 81%, as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.77 (dd, J = 4.2, 1.6 Hz, 1H), 8.72 (dd, J = 5.7, 3.3 Hz, 1H), 8.11 (dd, J = 8.2, 1.6 Hz, 1H), 7.56−7.50 (m, 2H), 7.41 (dd, J = 8.2, 4.2 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 3.65 (s, 3H), 3.37 (d, J = 13.6 Hz, 1H), 3.06 (d, J = 13.6 Hz, 1H), 2.22 (td, J = 13.1, 4.6 Hz, 1H), 1.87 (td, J = 13.1, 3.9 Hz, 1H), 1.62−1.49 (m, 2H), 1.40−1.29 (m, 1H), 0.89 (t, d, J = 6.3 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.6, 159.0, 148.7, 138.7, 136.0, 133.4, 131.0, 127.7, 127.0, 126.4, 122.6, 121.8, 120.4, 116.6, 113.8, 55.0, 53.2, 42.7, 35.4, 34.2, 28.0, 22.3; FTIR (neat) 3304, 2956, 2927, 2873, 2235, 1685, 1528, 1512, 1465, 1325, 1245, 1177, 1033, 9009, 825, 694 cm^{-1}; MS (ESI) m/z 402 (M + H)$^+$; HRMS (ESI) m/z calcd for $C_{25}H_{28}O_2N_3$ (M + H)$^+$ 402.2176, found 402.2176.

*2-(Bis(4-methoxyphenyl)methyl)-2-cyano-N-(quinolin-8-yl)-dodecanamide (**5k**).* To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar, were added the amide derivative (**3a**, 47 mg, 0.1 mmol), 4-iodoanisole (**2a**, 35 mg, 0.15 mmol), $Pd(OAc)_2$ (2.25 mg, 0.01 mmol), $Mn(OAc)_2$ (35 mg, 0.2 mmol), Na_2CO_3 (21 mg, 0.2 mmol), and *t*-AmOH (2 mL). The mixture was stirred for 40 h at 130 °C followed by cooling. The reaction mixture was diluted with EtOAc (5 mL), filtered through a pad of Celite, and concentrated under reduced pressure. Water (5 mL) was added to the crude residue and the product extracted with EtOAc (5 mL × 2). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent, hexane/EtOAc = 10:1) to afford the desired arylated product as a brown oil (**5k**, 11.5 mg) in 20% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.73 (s, 1H), 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.60 (dd, J = 7.3, 1.6 Hz, 1H), 8.13 (dd, J = 8.3, 1.6 Hz, 1H), 7.58−7.41 (m, 7H), 6.92 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 4.50 (s, 1H), 3.81 (s, 3H), 3.55 (s, 3H), 2.08 (td, J = 12.9, 4.4 Hz, 1H), 1.73 (td, J = 12.5, 4.0 Hz, 1H), 1.27−1.12 (m, 16H), 0.83 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.6, 158.8, 158.4, 148.8, 138.8, 136.0, 133.4, 131.8, 131.1, 130.3, 129.5, 127.7, 127.0, 122.6, 121.8, 121.1, 116.6, 114.2, 113.8, 56.3, 55.8, 55.2, 54.9, 37.4, 31.8, 30.9, 29.4, 29.3, 29.2, 29.2, 25.6, 22.6, 14.1; FTIR (neat) 3309,

DOI: 10.1021/acs.joc.5b02138
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2929, 2868, 2237, 1685, 1619, 1552, 1320, 1198, 1022, 901, 799 cm^{-1}; MS (ESI) m/z 578 $(M + H)^+$.

*2-Cyano-N-(quinolin-8-yl)-2,3-dihydro-1H-indene-2-carboxamide (**6**).* To an oven-dried 20 mL sealed tube were added amide derivative **1l** (176 mg, 0.4 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), $Mn(OAc)_2$ (138 mg, 0.8 mmol), Na_2CO_3 (85 mg, 0.8 mmol), and *t*-AmOH (4 mL) under a N_2 atmosphere. The mixture was stirred for 48 h at 130 °C followed by cooling. The reaction mixture was diluted with EtOAc (10 mL), filtered through a pad of Celite, and concentrated under reduced pressure. Water (10 mL) was added to the crude residue and the product extracted with ethyl acetate (6 mL × 2). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent, hexane/EtOAc = 15:1) to afford the title compound **6** as white solid (101 mg, 65%): mp 136−137 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.89 (s, 1H), 8.85 (dd, J = 4.2, 1.6 Hz, 1H), 8.70 (dd, J = 7.2, 1.6 Hz, 1H), 7.81 (dd, J = 8.3, 1.6 Hz, 1H), 7.61−7.52 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 7.32−7.26 (m, 4H), 3.89 (d, J = 15.8 Hz, 1H), 3.70 (d, J = 15.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.4, 148.8, 138.6, 138.5, 135.2, 133.5, 127.8, 127.7, 127.1, 124.6, 122.7, 122.0, 121.9, 116.8, 49.8, 43.7; FTIR (neat) 3308, 2922, 2850, 2237, 1682, 1524, 1477, 1323, 1257, 1062, 906, 8323, 796, 611 cm^{-1}; MS (ESI) m/z 314 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{20}H_{16}ON_3$ $(M + H)^+$ 314.1288, found 314.1288.

*2,2′-([2,2′-Bithiophene]-5,5′-diylbis(methylene))bis(2-cyano-N-(quinolin-8 yl)dodecanamide) (**7**).* To an oven-dried 20 mL sealed tube were added 5,5′-diiodo-2,2′-bithiophene **2t** (138 mg, 0.33 mmol), amide derivative **1a** (365 mg, 1 mmol), $Pd(OAc)_2$ (13 mg, 0.06 mmol), $Mn(OAc)_2$ (103 mg, 0.6 mmol), Na_2CO_3 (63 mg, 0.6 mmol), and *t*-AmOH (6 mL) under a N_2 atmosphere. The mixture was stirred for 48 h at 130 °C followed by cooling. The reaction mixture was diluted with EtOAc, filtered through a pad of Celite, and concentrated under reduced pressure. Water was added to the crude residue and the product extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent, hexane/EtOAc = 10:1) to afford the desired product 7 as a pale yellow oil (203 mg, 69%): ^1H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H), 10.75 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.75 (dd, J = 4.2, 1.6 Hz, 1H), 8.72−8.68 (m, 2H), 8.14−8.07 (m, 2H), 7.58−7.49 (m, 4H), 7.44−7.38 (m, 2H), 6.84 (dd, J = 5.4, 3.7 Hz, 2H), 6.74 (dd, J = 8.9, 3.6 Hz, 2H), 3.55 (dd, J = 14.6, 1.7 Hz, 2H), 3.25 (dd, J = 14.6, 2.8 Hz, 2H), 2.15 (dd, J = 16.3, 7.0 Hz, 2H), 1.89 (td, J = 12.8, 3.9 Hz, 2H), 1.72−1.56 (m, 2H), 1.52−1.40 (m, 2H), 1.37−1.15 (m, 28H), 0.84 (t, J = 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.2, 148.9, 138.7, 137.1, 137.1, 136.1, 136.0, 134.8, 134.8, 133.3, 133.3, 128.7, 127.8, 127.0, 123.5, 123.5, 122.8, 122.8, 121.9, 121.8, 120.1, 116.8, 116.8, 53.0, 52.9, 37.7, 37.6, 37.4, 31.8, 29.4, 29.4, 29.3, 29.2, 29.2, 25.6, 22.6, 14.1; FTIR (neat) 3301, 2923, 2853, 2235, 1686, 1528, 1485, 1424, 1326, 1170, 908, 825, 789, 756 cm^{-1}; MS (ESI) m/z 893 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{54}H_{65}O_2N_6S_2$ $(M + H)^+$ 893.4605, found 893.4604.

*2-Benzyl-3-(4-methoxyphenyl)-N-(quinolin-8-yl)propanamide (**8**).*[15a,20] Under an inert atmosphere, to a solution of SmI_2 (6 mL, 0.1 M in THF, 0.6 mmol) in a two-neck round-bottom flask was added HMPA (1 mL) at room temperature with stirring for 1 h. To the above solution, amide **4a** (84 mg, 0.2 mmol) in THF (2 mL) was added with stirring for 6 h. After completion of the reaction, the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL) and dried over anhydrous magnesium sulfate. The crude product was obtained after evaporation of solvent under reduced pressure using a rotary evaporator. The crude product was purified by column chromatography, providing the product **8** (36 mg, 45%) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.72 (dd, J = 7.4, 1.5 Hz, 1H), 8.64 (dd, J = 4.2, 1.7 Hz, 1H), 8.09 (dd, J = 8.4, 1.6 Hz, 1H), 7.56−7.42 (m, 2H), 7.38 (dd, J = 8.2, 4.2 Hz, 1H), 7.26−7.09 (m, 8H), 6.73 (d, J = 8.6 Hz, 2H), 3.67 (s, 3H), 3.20−3.07 (m, 2H), 3.03−2.97 (m, 1H), 2.93−2.83 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.1, 158.0, 147.8, 139.5, 136.1, 134.2, 131.5, 129.9, 128.9, 128.4, 127.7, 127.2, 126.2, 121.4, 121.3, 116.4, 114.0, 113.8, 55.1, 53.4, 38.6, 37.9; FTIR (neat) 3033, 2955, 2924, 1682, 1510, 1423, 1323, 1245, 1177, 1032, 824, 790 cm^{-1}; MS (ESI) m/z 397 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{26}H_{25}O_2N_2$ $(M + H)^+$ 397.1911, found 397.1911.

*Preparation of 2-Benzyl-3-(4-methoxyphenyl)propanamide (**9a**).*[16a] To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar, were added **4a** (84 mg, 0.2 mmol), KOH (45 mg, 0.8 mmol), and *tert*-amyl alcohol (1 mL) under a stream of argon. The vessel was sealed, and the mixture was stirred at 120 °C for 24 h. After cooling to room temperature, the mixture was passed through a pad of silica with copious washings with EtOAc (10 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:6) to afford **9a** (41 mg, 77%) as a white solid: mp 137−138 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.25 (m, 2H), 7.23−7.17 (m, 3H), 7.11 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.10 (s, 1H), 4.88 (s, 1H), 3.77 (s, 3H), 3.02−2.89 (m, 2H), 2.83−2.72 (m, 2H), 2.63−2.53 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.9, 158.1, 139.5, 131.4, 129.9, 128.9, 128.5, 126.4, 113.8, 55.2, 51.9, 38.7, 37.9; FTIR (neat) 3394, 3182, 3025, 2961, 2857, 1644, 1514, 1421, 1251, 1177, 1032, 824, 790 cm^{-1}; MS (ESI) m/z 270 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{17}H_{20}O_2N$ $(M + H)^+$ 270.1489, found 270.1489.

*Preparation of 2-Benzyl-3-(4-methoxyphenyl)propanoic acid (**9b**).*[16a] To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar, were added **4a** (84 mg, 0.2 mmol), KOH (45 mg, 0.8 mmol), and *tert*-amyl alcohol (1 mL) under a stream of argon. The vessel was sealed, and the mixture was stirred at 130 °C for 40 h. After cooling to room temperature, the solvent was removed, water (5 mL) was added, and pH adjusted to 4 using 2 N HCl. The aqueous layer was extracted with EtOAc (5 × 3 mL). The combined organic layers were washed with brine (10 mL), dried over Mg_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:4) to afford **9b** (35 mg, 65%) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.23 (m, 2H), 7.22−7.13 (m, 3H), 7.08 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H), 3.00−2.87 (m, 3H), 2.82−2.70 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 180.8, 158.1, 138.8, 130.7, 129.8, 128.9, 128.4, 126.5, 113.8, 55.2, 49.5, 37.6, 36.9; FTIR (neat) 3309, 2931, 1702, 1610, 1584, 1442, 1299, 1244, 1033, 825, 698 cm^{-1}; MS (ESI) m/z 269 $(M - H)^+$; HRMS (ESI) m/z calcd for $C_{17}H_{19}O_3$ $(M + H)^+$ 271.1329, found 271.1328.

General Procedure for the Preparation of 10a and 10b. To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar, were added arylated compound [**3a** (141 mg, 0.3 mmol) or **4a** (126 mg, 0.3 mmol)], KOH (67 mg, 1.2 mmol), and *tert*-amyl alcohol (2 mL) under a stream of argon. The vessel was sealed, and the mixture was stirred at 90 °C for 3 h. After cooling to room temperature, the mixture was concentrated in vacuo, the residue was dissolved in 5 mL of water, and the pH was adjusted to 4 using 1 N HCl. The product was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL) and dried over anhydrous magnesium sulfate followed by evaporation of solvent under reduced pressure to give a pale yellow oil. The crude oil was purified by column chromatography on silica gel (EtOAc/hexane = 1:3) to give the corresponding acid.

*2-Cyano-2-(4-methoxybenzyl)dodecanoic Acid (**10a**).* Yield of 82 mg, 79%, as a white solid; mp 52−53 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (bs, 1H), 7.21 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 3.17 (d, J = 13.7 Hz, 1H), 3.04 (d, J = 13.7 Hz, 1H), 2.03−1.94 (m, 1H), 1.87−1.78 (m, 1H), 1.68−1.57 (m, 1H), 1.44−1.20 (m, 15H), 0.88 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.2, 159.2, 131.0, 125.8, 118.4, 114.0, 55.2, 52.2, 42.2, 37.0, 31.9, 29.5, 29.4, 29.3, 29.2, 25.5, 22.7, 14.1; FTIR (neat) 3035, 2922, 2840, 1695, 1512, 1249, 1030, 828, 698 cm^{-1}; MS (ESI) m/z 346 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{21}H_{32}O_3N$ $(M + H)^+$ 346.2377, found 346.2373.

*2-Benzyl-2-cyano-3-(4-methoxyphenyl)propanoic Acid (**10b**).* Yield of 67 mg, 75%, as a white solid; mp 121−122 °C; ^1H NMR

DOI: 10.1021/acs.joc.5b02138
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(400 MHz, $CDCl_3$) δ 9.49 (bs, 1H), 7.35−7.27 (m, 5H), 7.22 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 3.78 (s, 3H), 3.28 (dd, J = 13.5, 11.0 Hz, 2H), 3.10 (dd, J = 13.8, 12.1 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.4, 159.3, 133.6, 131.1, 129.9, 128.7, 128.0, 125.5, 117.9, 114.1, 55.2, 53.9, 42.7, 42.2; FTIR (neat) 3165, 2954, 2914, 2841, 2248, 1737, 1612, 1514, 1301, 1241, 1018, 819, 721 cm^{-1}; MS (ESI) m/z 296 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{18}H_{18}O_3N$ $(M + H)^+$ 296.1281, found 296.1279.

General Procedure for Detachment of Directing Group (11a and 11b).[8f] To an oven-dried 10 mL screw-capped vial were added arylated compound [**3a** (235 mg, 0.5 mmol) or **4a** (210 mg, 0.5 mmol)] and 2 M HCl in MeOH (5 mL) under a gentle stream of argon. The mixture was stirred for 20 h at 65 °C followed by cooling. The mixture was concentrated in vacuo and the residue was subjected to column chromatography on silica gel to afford the corresponding α-cyano methyl ester.

*Methyl 2-Cyano-2-(4-methoxybenzyl)dodecanoate (**11a**).* Yield of 129 mg, 72%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 3.69 (s, 3H), 3.14 (d, J = 13.6 Hz, 1H), 2.99 (d, J = 13.6 Hz, 1H), 1.99 (t, J = 14.6 Hz, 1H), 1.80 (d, J = 12.6 Hz, 1H), 1.66−1.53 (m, 1H), 1.36−1.20 (m, 15H), 0.88 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 159.2, 130.9, 126.3, 119.1, 113.9, 55.2, 53.2, 52.0, 42.6, 37.1, 31.9, 29.5, 29.4, 29.3, 29.2, 25.5, 22.7, 14.1; FTIR (neat) 3029, 2924, 1725, 1619, 1519, 1309, 1257, 1031, 835, 704 cm^{-1}; MS (ESI) m/z 360 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{22}H_{34}O_3N$ $(M + H)^+$ 360.2533, found 360.2531.

*Methyl 2-Benzyl-2-cyano-3-(4-methoxyphenyl)propanoate (**11b**).* Yield of 125 mg, 81%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 7.20 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 3.78 (s, 3H), 3.54 (s, 3H), 3.29 (dd, J = 13.5, 10.6 Hz, 2H), 3.06 (t, J = 13.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.8, 159.2, 134.1, 31.0, 129.9, 128.6, 127.9, 126.0, 118.6, 114.0, 55.2, 53.7, 53.1, 43.1, 42.6; FTIR (neat) 3022, 2953, 1720, 1613, 1551, 1454, 1321, 1246, 1032, 837, 702 cm^{-1}; MS (ESI) m/z 310 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{19}H_{20}O_3N$ $(M + H)^+$ 310.1438, found 310.1434.

*Synthesis of 2-(((tert-Butoxycarbonyl)amino)methyl)-2-(4-methoxybenzyl)dodecanoic Acid (**12a**).* A stirred mixture of α-cyano acid (**10a**, 35 mg, 0.1 mmol), MeOH (3 mL), $(Boc)_2O$ (24 mg, 0.11 mmol), DIPEA (15 mg, 0.11 mmol), and Pd catalyst (10 wt % on activated charcoal, 1.05 mg, 0.01 mmol) was hydrogenated at ambient temperature at 50 psi for 36 h. The catalyst was then filtered off and washed with MeOH and the solvent evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1:4) to give the *N*-Boc-β-amino acid **12** (26 mg) in 59% yield as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.3 Hz, 2H), 4.93 (bs, 1H), 3.77 (s, 3H), 3.41−3.30 (m, 1H), 3.29−3.16 (m, 1H), 2.97 (d, J = 13.6 Hz, 1H), 2.80 (d, J = 13.9 Hz, 1H), 1.66−1.41 (m, 11H), 1.33−1.18 (m, 16H), 0.87 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 181.8, 158.4, 156.0, 131.0, 128.4, 113.6, 79.4, 55.1, 51.2, 43.4, 39.6, 34.3, 31.9, 30.2, 29.7, 29.6, 29.4, 29.3, 28.4, 24.0, 22.7, 14.1; FTIR (neat) 3324, 3081, 2929, 1732, 1615, 1574, 1422, 1052, 833, 795, 782 cm^{-1}; MS (ESI) m/z 448 $(M - H)^+$.

*Synthesis of 2-Benzyl-3-((tert-butoxycarbonyl)amino)-2-(4-methoxybenzyl)propanoic Acid (**12b**).* A stirred mixture of α-cyano acid (**10b**, 30 mg, 0.1 mmol), MeOH (3 mL), $(Boc)_2O$ (24 mg, 0.11 mmol), DIPEA (15 mg, 0.11 mmol), and Pd catalyst (10 wt % on activated charcoal, 1.05 mg, 0.01 mmol) was hydrogenated at ambient temperature at 50 psi for 40 h. The catalyst was then filtered off and washed with MeOH, and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1:4) to give the *N*-Boc-β-amino acid **12b** (22 mg) in 55% yield as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.16 (m, 5H), 7.14−7.06 (m, 2H), 6.80 (d, J = 8.5 Hz, 2H), 5.01 (bs, 1H), 3.76 (s, 3H), 3.32−3.03 (m, 4H), 2.79 (dd, J = 13.7, 10.7 Hz, 2H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 180.9, 158.6, 156.2, 136.2, 131.4, 130.3, 128.3, 127.9, 126.8, 113.7, 79.5, 55.1, 53.4, 42.9, 41.2, 40.4, 28.4; FTIR (neat) 3351, 3029, 2921, 1734, 1619, 1578, 1422, 1081, 837, 795, 780 cm^{-1}; MS (ESI) m/z 400 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{23}H_{30}O_5N$ $(M + H)^+$ 400.2118, found 400.2118.

General Procedure for the Preparation of β-Amino Esters (13a and 13b).[21] A stirred mixture of α-cyano ester [**11a** (108 mg, 0.3 mmol) or **11b** (93 mg, 0.3 mmol)], MeOH (3 mL), 1 M HCl in diethyl ether (50 μL), and Pd catalyst (10 wt % on activated charcoal, 3.2 mg, 0.03 mmol) was hydrogenated at ambient temperature at 50 psi for 24 h. The catalyst was then filtered off and washed with MeOH and the filtrate was evaporated. To the oily residue was added saturated $NaHCO_3$ solution and the product extracted with EtOAc (10 mL × 2). The combined organic extracts were dried over Mg_2SO_4 and evaporated. The residue was purified by flash chromatography to give the corresponding β-amino ester.

*Methyl 2-(Aminomethyl)-2-(4-methoxybenzyl)dodecanoate (**13a**).* Yield of 89 mg, 82%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H), 3.67 (s, 3H), 2.92 (d, J = 13.8 Hz, 1H), 2.82 (d, J = 13.8 Hz, 1H), 2.77 (bs, 2H), 1.59−1.43 (m, 2H), 1.41−1.19 (m, 18H), 0.88 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.5, 158.2, 130.8, 129.4, 113.5, 55.1, 52.8, 44.5, 38.1, 33.1, 31.9, 30.1, 29.6, 29.5, 29.5, 29.3, 24.2, 22.7, 14.1; FTIR (neat) 3391, 3033, 2929, 1722, 1610, 1511, 1454, 1176, 1081, 833, 794, 740 cm^{-1}; MS (ESI) m/z 364 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{22}H_{38}O_3N$ $(M + H)^+$ 364.2846, found 364.2842.

*Methyl 3-amino-2-benzyl-2-(4-methoxybenzyl)propanoate (**13b**).* Yield of 81 mg, 80%, as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.18 (m, 3H), 7.16−7.12 (m, 2H), 7.06 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 3.77 (s, 3H), 3.64 (s, 3H), 3.09 (dd, J = 16.6, 13.7 Hz, 2H), 2.84 (t, J = 13.7 Hz, 2H)2.71 (bs, 2H), 1.16 (bs, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.7, 158.2, 137.4, 130.9, 129.9, 129.2, 128.2, 126.5, 113.6, 55.1, 54.0, 51.4, 42.3, 40.7, 39.8; FTIR (neat) 3395, 3029, 2929, 1721, 1618, 1511, 1450, 1300, 1246, 1031, 833, 701 cm^{-1}; MS (ESI) m/z 314 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{19}H_{24}O_3N$ $(M + H)^+$ 314.1751, found 314.1750.

*Synthesis of 3-Amino-2,2-dibenzylpropan-1-ol (**14**).*[22] A suspension of $LiAlH_4$ (0.5 mL, 1 M solution in THF, 0.5 mmol) in THF (4 mL) was cooled to 0 °C and stirred, while a solution of **4c** (78 g, 0.2 mmol) in THF (2 mL) was added dropwise under argon. After addition was completed, the vessel was equipped with a water-jacketed condenser, and the mixture was refluxed for 7.5 h under argon and then quenched by cautious addition of H_2O (1 mL) while being cooled in an ice bath. The mixture was filtered through a thin pad of Celite and washed with Et_2O (10 mL), and the combined filtrate was concentrated in vacuo. The crude residue was purified by flash chromatography using EtOAc/hexanes = 1:3, yielding the title compound as a white solid (37 mg, 72%): mp 112−113 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.14 (m, 10H), 3.60 (s, 2H), 3.47 (s, 1H), 2.83 (t, J = 6.6 Hz, 4H), 2.57 (d, J = 13.4, 2H), 2.40 (bs, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 137.6, 130.6, 128.0, 126.2, 68.5, 49.3, 41.8, 40.4; FTIR (neat) 3369, 3025, 2916, 2854, 1581, 1494, 1443, 1390, 1114, 1054, 697 cm^{-1}; MS (ESI) m/z 256 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{17}H_{22}ON$ $(M + H)^+$ 256.1696, found 256.1696.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02138.

Copies of ^1H and $^{13}C\{^1H\}$ NMR spectra (DOCX)

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.joc.5b02138
J. Org. Chem. 2015, 80, 11447−11459

■ ACKNOWLEDGMENTS

This research was funded by Union University. The authors are grateful for the HRMS data provided by D. R. Phillips and C.-W. Chou [Proteomics and Mass Spectrometry (PAMS) Facility, NIH grant 1S10RR1028859] at the University of Georgia, Department of Chemistry, Athens, Georgia.

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DOI: 10.1021/acs.joc.5b02138
J. Org. Chem. 2015, 80, 11447−11459