Cesium Effect: High Chemoselectivity in Direct N-Alkylation of Amines

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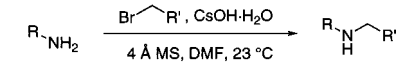
A novel method for the mono-N-alkylation of primary amines, diamines, and polyamines was developed using cesium bases in order to prepare secondary amines efficiently. A cesium base not only promoted alkylation of primary amines but also suppressed overalkylations of the produced secondary amines. Various amines, alkyl bromides, and alkyl sulfonates were examined, and the results demonstrated this methodology was highly chemoselective to favor mono-N-alkylation over dialkylation. In particular, use of either sterically demanding substrates or amino acid derivatives afforded the secondary amines exclusively, offering wide applications in peptidomimetic syntheses.

Introduction

Amines and their derivatives are prevalent functionalities in various natural products and unnatural synthetic targets. Due to its unique biological properties, the amine moiety has played a central role in chemotherapeutics of numerous diseases.[1] Polyamines and peptidomimetics have constituted some of the most popular targets in recent combinatorial approaches in drug development.[2] In particular, the synthesis of secondary amines has long been of interest because of their potential as robust pharmacophores and as useful synthetic intermediates.[3] General synthetic methods for the preparation of dialkylamines[4] have included direct N-alkylation,[5] amide reduction,[6] or the more popular reductive amination protocol.[7] Although these methods are quite reliable, practical success has been relatively limited since concomitant overalkylations are a common impediment. To avoid this problem using traditional techniques, the rather expensive amine has been used in large excess, and further purification to remove the starting amine is necessary.[8] Use of N-protecting groups has been a typical way to avert these shortcomings, although they add lengthy synthetic steps in desired transformations.[9] Therefore, considerable interest exists in developing efficient protocols for the construction of carbon−nitrogen bonds.

Scheme 1



Previously, we described a highly useful method using cesium hydroxide for the chemoselective N-alkylation of primary amines, which afforded secondary amines predominantly or exclusively.[10] Primary amines united with various bromides to produce the secondary amines in high yields using powdered dry 4 Å molecular sieves in *N*,*N*-dimethylformamide (DMF) (Scheme 1). Observed selectivities between mono- and dialkylations were typically on the order of 9:1, respectively, or higher, which is far superior to existing protocols. This methodology has been successfully employed as demonstrated in Wipf's asymmetric synthesis of the 1,2,3,4-tetrahydroisoquinoline moiety of the antitumor antibiotic tetrazomine.[11] In this paper, we elaborate upon in further detail with regards to the scope of the synthetic utility as well as our results toward applications and novel mechanistic concepts.

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(1) (a) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Tetrahedron* **1992**, *48*, 4475. (b) For a recent review of the various biological activities of polyamines, see: Blagbrough, I. S.; Carrington, S.; Geall, A. J. *Pharm. Sci.* **1997**, *3*, 223. (c) Bergeron, R. J.; Feng, Y.; Weimer, W. R.; McManis, J. S.; Dimova, H.; Porter, C.; Raisler, B.; Phanstiel, O. *J. Med. Chem.* **1997**, *40*, 1475.

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(3) Inaf, S. S.; Witiak, D. T. *Synthesis* **1999**, 435.

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(5) (a) Spialter, L.; Pappalardo, J. A. In *The Acyclic Aliphatic Tertiary Amines*; The Macmillan Co.: New York, 1965; p 14. (b) O'Meara, J. A.; Gardee, N.; Jung, M.; Ben, R. N.; Durst, T. *J. Org. Chem.* **1998**, *63*, 3117. (c) Koh, K.; Ben, R. N.; Durst, T. *Tetrahedron Lett.* **1993**, *34*, 4473. (d) Valot, F.; Fache, F.; Jacquot, R.; Spagnol, M.; Lemaire, M. *Tetrahedron Lett.* **1999**, *40*, 3689. (e) Suga, K.; Watanabe, S.; Fujita, T.; Pan, T. P. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3606.

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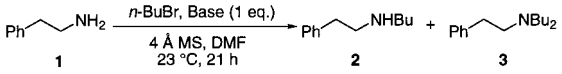
Table 1. N-Alkylation of Phenethylamine Using Various Bases



entry	base	yield of **2** (%)	yield of **3** (%)	ratio (**2**/**3**)
1	LiOH	62	21	3:1
2	NaOH	51	26	2:1
3	KOH	55	29	2:1
4	KOH/18-c-6	75	21	4:1
5	RbOH	65	24	3:1
6	CsOH	89	10	9:1
7	Cs_2CO_3	30	40	~1:1
8	$CsHCO_3$	26	18	~1:1
9	CsF	20	19	~1:1

Results and Discussion

Cesium Effect: Various Aspects. At the outset of this work, we began our approach by screening a variety of different bases for efficient mono-N-alkylation conditions. Numerous alkali bases were probed including lithium, sodium, potassium, rubidium, and cesium hydroxide for the efficient coupling of phenethylamine **1** using a slight excess of 1-bromobutane (1.2 equiv) as an initial substrate (Table 1). Of the various alkali hydroxides examined, cesium hydroxide was the most successful base (Table 1, entry 6), offering the greatest selectivity in terms of delivering the dialkylamine **2**, which in turn also purportedly minimized polyalkylations (e.g., **3**). In comparison, other bases gave poor selectivities (Table 1, entries 1−3 and 5), whereas addition of a crown ether improved the yield of the desired secondary amine marginally (Table 1, entry 4). We attribute this high chemoselectivity in favor of the secondary amine as further evidence of the unprecedented "cesium effect",[12] which we have observed in our previous O-alkylation protocols.[13] Furthermore, since cesium hydroxide was found to be far superior, other cesium bases were investigated in the hope to improve the selectivity. Much to our disappointment, using 1 equiv of other cesium bases such as cesium carbonate (Table 1, entry 7), cesium bicarbonate (Table 1, entry 8), and cesium fluoride (Table 1, entry 9) gave low conversions, presumably due to decreased basicities and solubilities. In addition, the use of organic bases as additives (e.g., Et_3N and DBU) in the presence of cesium hydroxide offered no greater selectivity.

Next, our attention was directed toward solvent effects for efficient cesium hydroxide mediated N-alkylation reactions. When various solvents were examined, anhydrous DMF was found to be the solvent of choice, whereas other dry polar aprotic solvents including dimethyl sulfoxide (DMSO), 1-methyl-2-pyrrolidinone (NMP), and *N*,*N*-dimethylacetamide (DMAC) were found to be comparable in terms of offering highest yields of **2** (Table 2). However, other solvents including nitromethane, acetonitrile, ethanol, ether, acetone, toluene, methylene chloride, and wet DMF were less suitable since the starting material **1** was recovered predominantly.

Table 2. Use of Various Solvents in Cesium Base-Promoted N-Alkylation of 1

entry	solvent	yield of **2** (%)	yield of **3** (%)	ratio (**2**/**3**)
1	DMF	89	10	9:1
2	DMSO	70	11	7:1
3	NMP	82	10	8:1
4	DMAC	75	13	6:1

Table 3. Use of Various Additives in CsOH-Promoted N-Alkylation of 1

entry	additive	yield of **2** (%)	yield of **3** (%)
1	none	59	12
2	none[a]	90	10
3	Al_2O_3[b]	54	16
4	desiccant[c]	58	18
5	3 Å MS[d]	60	14
6	4 Å MS	89	10
7	5 Å MS	83	12
8	TBAI[e]	66	7
9	TBAHS[f]	62	18

[a] $CsOH·H_2O$ was dried at 120 °C for 24 h. [b] Activated neutral alumina (50−200 mesh). [c] EM Science silica desiccant (6−8 mesh). [d] Powdered molecular sieves were activated by drying at 120 °C for 24 h prior to use. [e] TBAI = tetrabutylammonium iodide. [f] Tetrabuylammonium hydrogen sulfate.

Based on this result, it was found that the inclusion of a drying agent such as activated powdered 4 Å molecular sieves accelerated the alkylation as well as improved the selectivity and yield of the secondary amine.[14] This result can be attributed to the removal of adventitious water from the reaction media, which presumably can slow the reaction rate and diminish selectivity. Therefore, various drying agents were screened for high conversion and selectivity in favor of the secondary amine (Table 3). In the absence of a desiccant, butylphenethylamine **2** was still formed in moderate yield (Table 3, entry 1). However, when CsOH was scrupulously dried, the yield of the dialkylamine increased dramatically, further implying the need for anhydrous conditions (Table 3, entry 2). Using commercially available $CsOH·H_2O$, in combination with various additives such as neutral alumina (entry 3) or desiccant (Table 3, entry 4) offered analogous results to entry 1. Also, the use of activated molecular sieves of various pore sizes (3, 4, and 5 Å; Table 3, entries 5−7) proved to be facile and pragmatic. Furthermore, use of onium salts such as tetrabutylammonium iodide (TBAI) (Table 3, entry 8) or tetrabutylammonium hydrogen sulfate (TBAHS) (Table 3, entry 9), which facilitated our etherifications,[15] was found to exert an opposite effect by retarding the N-alkylations and offering the desired dialkylamine in low yields.

More importantly, since cesium hydroxide was found to have a marked effect on the N-alkylation of primary amines, and also deterred the formation of tertiary amines, it became imperative to subject the secondary amine to a comparative alkylation study. As delineated in Scheme 2, dialkylamine **2** was submitted to our N-alkylation protocol, barely offering the tertiary amine **3** (10%) while most of the starting material **2** was

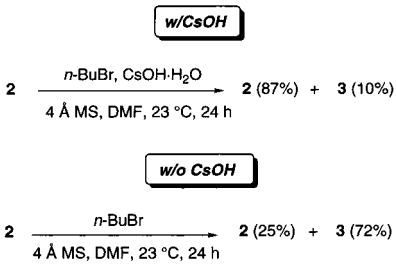
(12) For reviews on the "cesium effect", see: (a) Ostrowicki, A.; Vögtle, F. In *Topics In Current Chemistry*; Weber, E., Vögtle, F., Eds.; Springer-Verlag: Heidelberg, 1992; Vol. 161; p 37. (b) Galli, C. *Org. Prep. Proced. Int.* **1992**, *24*, 287 and references therein. (c) Blum, Z. *Acta Chem. Scand.* **1989**, *43*, 248.

(13) For our O-alkylations, see: (a) Parrish, J. P.; Dueno, E. E.; Kim, S.-I.; Jung, K. W. *Synth. Commun.* **2000**, *30*, 2687. (b) Parrish, J. P.; Sudaresan, B.; Jung, K. W. *Synth. Commun.* **1999**, *29*, 4423. (c) Chu, F.; Kim, S.-I.; Dueno, E. E.; Jung, K. W. *Tetrahedron Lett.* **1999**, *40*, 1847. (d) Kim, S.-I.; Chu, F.; Dueno, E. E.; Jung, K. W. *J. Org. Chem.* **1999**, *64*, 4578.

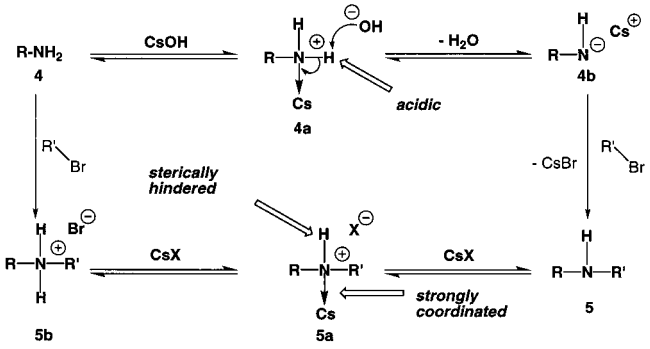
(14) When molecular sieves were not activated, yields and selectivities diminished. Reactions were sluggish to result in recovery of the starting amine predominantly.

(15) Dueno, E. E.; Chu, F.; Kim, S.-I.; Jung, K. W. *Tetrahedron Lett.* **1999**, *40*, 1843.

Scheme 2



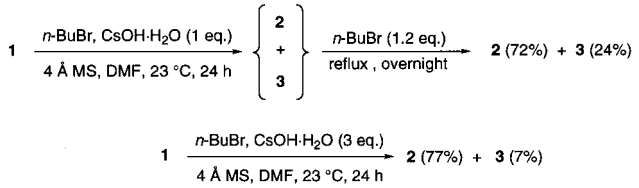
Scheme 3



recovered unreacted in 87% yield after 24 h. On the contrary, in the absence of cesium hydroxide, overalkylation readily proceeded giving rise to the preparation of **3** in high yield (72%). This important highlight implied that primary and secondary amines exert opposing reactivities in the presence of cesium hydroxide, suggesting that the high chemoselectivity stems from reversal of normally observed alkylation rates. Rationale for enhanced chemoselectivities in N-alkylations is suggested in Scheme 3.

When **4** was stirred in the presence of $CsOH \cdot H_2O$ (1 equiv) in DMF containing activated powdered 4 Å molecular sieves for 30 min, amine−cesium complex **4a** could be provided since the cesium ion can behave as a Lewis acid, coordinating to primary amine **4** via a soft acid−soft base interaction (Scheme 3).[16] In a polar aprotic solvent such as DMF, the cesium ion is weakly coordinated to the hydroxide anion, therefore such a proximal effect with the amine seems reasonable.[17] Therefore, amine protons in complex **4a** should be sufficiently acidic to be abstracted by the hydroxide,[18] leading to the formation of cesium amide **4b** upon subsequent removal of water using molecular sieves as a desiccant. As demonstrated in our O-alkylations,[15] such anionic species constitute "naked anions" which enhance anion nucleophilicities. Thus, amide **4b** would react rapidly with the bromide, generating secondary amine **5**. As a consequence of inherently stronger basicity, dialkylamines should presumably coordinate to the cesium ion more strongly than the corresponding primary amines, which would lead to the formation of the relatively more stable complex **5a**. Owing to the increased sterics of quaternary salt **5a**, abstraction of available protons by hydroxide would be minimized, thus inhibiting the alkylation of secondary amines.[19] Also, stronger coordination exhibited in **5a** could help suppress further alkylation by reducing the nucleophilicity of the secondary amine, thereby allowing full consumption of the primary amine **4**.[20] Experimental evidence demonstrated in Scheme 2 lends further credence in support of our hypothesis. On the basis of this rationale, chemoselectivity in favor of secondary amines would be enhanced by the presence of heteroatoms, which in turn, can increase the coordinating ability of **5a**. Examples illustrating this phenomenon are elaborated in more details below. Moreover, steric elements would also augment the chemoselectivity in amine alkylations as well, which is also discussed in depth.

Scheme 4



To gain further insight about the role cesium hydroxide plays during the course of the reaction, an experiment was performed under intentionally harsh conditions. A crude mixture of secondary amine **2** and tertiary amine **3**, which were subsequently formed using the developed methodology, was treated with excess 1-bromobutane, and the reaction was allowed to proceed overnight at reflux in order to purposely overalkylate **2**. Remarkably, dialkylamine **2** was sluggish to undergo transformation to **3** despite its exposure to elevated temperature and excess halide, further providing evidence that these conditions are highly chemoselective in favor of secondary amine formation (Scheme 4). Since cesium hydroxide has convincingly shown to be excellent at diverting tertiary amine formation, a separate experiment was conducted in which the equivalents of base was increased in hopes to improve both the yield and ratio of **2**. As expected, the addition of more equivalents of cesium hydroxide (3 equiv) further suppressed tertiary amine formation, however, yields of the secondary amine slightly diminished as well (Scheme 4). Although the details for the exact origin of the reversal in N-alkylation selectivity are not proven yet, our conditions reported herein are strikingly efficient, offering universal applications that will be of prime interest to the synthetic community.

Using Various Electrophiles. As delineated in Table 4, primary and secondary bromides were examined and found to be generally applicable to the newly developed techniques. Various bromides were efficiently united with phenethylamine **1**, generating the corresponding secondary amines predominantly or exclusively depending on the nature of the bromide. As depicted in entry 1 (Table

(16) (a) Constable, E. C. In *Metals and Ligand Reactivity*; VCH Publishers: New York, 1996; p 102. (b) Dehmlow, E. V.; Thieser, R.; Zahalka, H. A.; Sasson, Y. *Tetrahedron Lett.* **1985**, *26*, 297. (c) Santhanalakshmi, J.; Raja, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2829. (d) Ando, T.; Yamawaki, J. *Chem. Lett.* **1979**, 45. (e) Onaka, M.; Ishikawa, K.; Izumi, Y. *Chem. Lett.* **1982**, 1783. (f) Blum, Z. *Acta Chem. Scand.* **1989**, *43*, 248. (g) Soong, L.-L.; Leroi, G. E.; Popov, A. I. *J. Solut. Chem.* **1989**, *18*, 561.

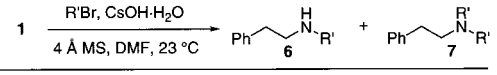
(17) Formation of "naked anions" by solvation of cesium ions has been previously postulated and studied extensively: Dijkstra, G.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1987**, *52*, 4230.

(18) For a similar case displaying how *N*-chelation increases the acidity of amine protons in order to provide a convenient method for regioselective mono-N-alkylation, see: (a) Bar-Haim, G.; Kol, M. *Tetrahedron Lett.* **1998**, *39*, 2643. (b) Bar-Haim, G.; Kol, M. *J. Org. Chem.* **1997**, *62*, 6682. (c) Bar-Haim, G.; Shach, R.; Kol, M. *Chem. Commun.* **1997**, 229.

(19) For a discussion on steric effects for deprotonation of ammonium salts: Jones, R. A. In *Quaternary Ammonium Salts Their Use in Phase-Transfer Catalysis*; Academic Press: New York, 2001.

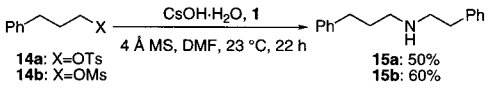
(20) Laplante, C.; Hall, D. G. *Org. Lett.* **2001**, *3*, 1487.

Table 4. CsOH-Promoted N-Alkylation of Primary Amine 1 with Various Bromides

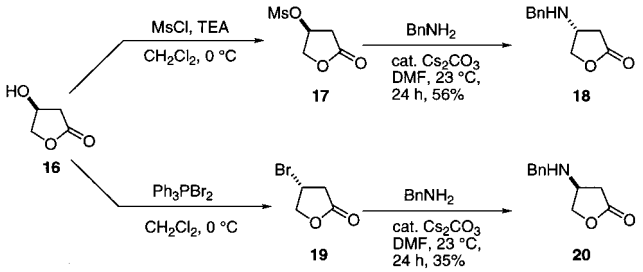


entry	bromide (R'Br)		CsOH·H_2O	time	yield (**6**)	yield (**7**)
1		(**8**)	1 eq	24 h	85%	10%
2		(**9**)	0.1 eq	4.5 h	85%	15%
3	BnBr	(**10**)	0.1 eq	4 h	85%	15%
4		(**11**)	3 eq	24 h	74%	0%
5		(**12**)	3 eq	48 h	80%	0%
6		(**13**)	3 eq	24 h	70%	0%

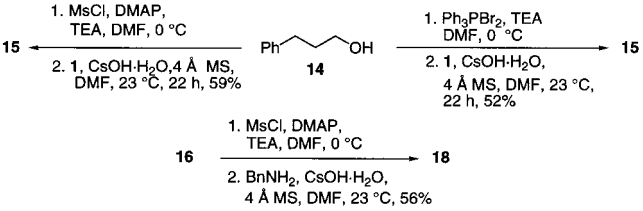
Scheme 5



Scheme 6



Scheme 7



4), 1-bromo-3-phenylpropane **8**, an unreactive bromide, underwent substitution easily to provide the desired secondary amine in high yield (85%) after 24 h with accompaniment by the trialkylamine (10%). Activated halides including allyl bromide **9** and benzyl bromide **10** offered similar yields (85%) over short reaction times, and proceeded efficiently with the use of a catalytic amount of cesium hydroxide (Table 4, entries 2 and 3). However, if more than a catalytic amount of cesium hydroxide was used, overalkylation became more prominent due to the highly reactive nature of these electrophiles. Interestingly, introduction of sterically hindered substituents such as the isobutyl moiety gave rise to the mono-N-alkylation product exclusively (Table 4, entry 4). As expected, sterically more demanding secondary bromides including 2-bromobutane **12** and isopropyl bromide **13** (Table 4, entries 5 and 6) followed similar suite, delivering the corresponding N-substituted amines as the sole product. As observed under previous conditions, tertiary bromides were resistant to alkylations under these conditions, indicating that introduction of steric elements suppresses overalkylation completely.

In view of these successful results, attention was turned to N-alkylations using various electrophiles to demonstrate substrate versatility. Since alcohols are key synthetic intermediates in numerous syntheses, we decided to perform the procedure using sulfonates. Tosylate (**14a**) and mesylate (**14b**) of 3-phenyl-1-propanol were easily prepared by known procedures.[21,22] The successful conversion of **14a** and **14b** into the corresponding secondary amines **15a** and **15b**, respectively, was accomplished by subjecting **1** to the usual N-alkylation conditions. After 22 h, **1** was found to react with the tosylate and mesylate in good yields (Scheme 5). Disappointingly, the triflate analogue proved problematic under these reaction conditions, offering the desired product along with a concomitant mixture of side products. These protocols are however highly chemoselective, averting common side reactions such as elimination, and background secondary alkylations were minimized (<15%).

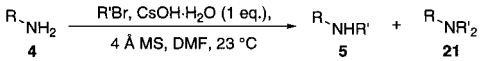
(21) Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 1179.
(22) Furst, A.; Koller, F. *Helv. Chim. Acta* **1947**, *30*, 1454.

Due to the importance as chiral synthons, chiral alcohols encompassing γ-butyrolactone **16** were also applied to the same sequence to afford the corresponding appropriate leaving groups for the ensuing direct N-alkylation (Scheme 6). Mesylate lactone **17** reacted smoothly with benzylamine using a catalytic amount of cesium carbonate to afford the N-benzylated lactone **18** in good yield. Likewise, bromination of the alcohol functionality using Ph_3PBr_2 at 0 °C gave rise to **19** followed by gentle treatment with benzylamine using the same reaction conditions, generating the secondary chiral amine **20** in an unoptimized yield (35%) after 24 h. In both examples, upon formation of a Mosher's amide with **18** or **20**, no racemization was observed within our detection limits, offering potential applications toward future drug design and synthesis.

The synthetic scope of this transformation of alcohols directly to secondary amines was further probed by a one-pot mesylation (or bromination) followed by sequential addition of the amine. Using the conditions described above, 3-phenyl-1-propanol **14** was successfully transformed into the corresponding bromide or mesylate, respectively. Upon consumption of the starting alcohol (monitored by TLC), phenethylamine (1 equiv) was added along with a catalytic amount of cesium base. In both synthetic sequences, after workup and purification, secondary amine **15** was isolated in acceptable yields, and isolation of intermediates proved unnecessary. Similar trends were noted using the one-pot alkylation of the hydroxy-butyrolactone substrate **16**, which also proved to be facile (Scheme 7).

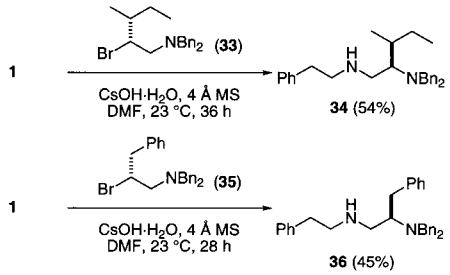
Use of Diverse Amines. Having bestowed high chemoselectivities in the reaction of **1** with various bromides (Table 4), it was next confirmed that the N-alkylation was applicable with the use of a range of different amines, offering similar trends (Table 5). Benzylamine **22**, a reactive amine, underwent consolidation with lipophilic bromides to offer the secondary amines as the major products (Table 5, entries 1 and 2). Primary alkylamines (Table 5, entry 3), as well as cycloalkylamines (Table 5, entries 4−6) subsequently proved pragmatic. Consequently, N-alkylation of more sterically demanding amines smoothly furnished the desired products exclusively (Table 5, entries 7−10). Much to our

Table 5. CsOH-Promoted N-Alkylation of Various Amines



entry	amine (RNH_2)	bromide (R' Br)	time (h)	yield of **5** (%)	yield of **21** (%)
1	$BnNH_2$ (**22**)	1-bromobutane (**23**)	24	83	10
2	**22**	1-bromooctane (**24**)	22	75	13
3	octylamine (**25**)	**8**	22	80	10
4	$C_6H_{11}CH_2NH_2$ (**26**)	**8**	22	90	10
5	cyclopropylamine (**27**)	**8**	18	83	12
6	cyclooctylamine (**28**)	**8**	22	75	10
7	1-adamantanamine (**29**)	**8**	18	82	0
8	**29**	(*E*)-cinnamyl bromide (**30**)	18	66	0
9	$^tBuNH_2$ (**31**)	**8**	24	90	0
10	*tert*-octylamine (**32**)	**10**	12	87	0
11	**25**	**23**	24	93	0

Scheme 8

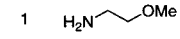
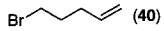
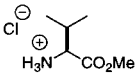


surprise, reaction of *n*-octylamine with 1-bromobutane was completely selective in generating the dialkylamine solely.

Synthesis of Peptidomimetics. Since the synthesis of higher order peptidomimetics and artificial biomolecular targets was one of the goals in mind, we decided to subject building blocks **33** and **35** to our developed N-alkylation techniques. After preparation of the respective *N*,*N*-dibenzylamino bromides via our previously reported bromination protocol,[23] these halides were successfully coupled with **1** under the standard conditions, affording the desired N-alkylated products (**34** and **36**) (Scheme 8). In each case, the secondary bromide was rearranged to the desired primary form via the corresponding aziridinium salt during the N-alkylation with phenethylamine.[24] In both entries, no overalkylations were detected. Also, as further evidence the synthesized product **36** was compared to the secondary amine formed via reductive amination ($NaCNBH_3$) using phenethylamine and the corresponding aldehyde of phenylalanine and found to be identical.

Given the generally superior performance of this method in terms of yields and selectivities, the feasibility using other amino acid derivatives was explored. As demonstrated in Table 6, N-alkylation of a β-amino ether (Table 6, entry 1) gave rise to a mixture of secondary and tertiary amines in 84% and 15%, respectively, presumably mimicking the aforementioned unhindered amines. Amazingly, the amino alcohols valinol **38** and isoleucinol **39** underwent smooth coupling to afford *N*-monoalkylated products exclusively due to the synergetic effect of strong coordination to the cesium ion as well as steric demands from side chains. *N*-alkylations using both an active halide such as **10** and unreactive bromides **33** progressed

Table 6. Chemoselective N-Alkylation of Amino Acid Derivatives

entry	amine (RNH_2)	bromide (R'Br)	conditions[a]	yield[b]
1	 (**37**)	**8**	1 eq., 22 h	84%[c]
2	Valinol (**38**)	**10**	0.1 eq., 12 h	74%
3	Isoleucinol (**39**)	**33**	1.0 eq., 36 h	52%
4		 (**40**)	1.1 eq., 5 h	65%
5	 (**41**)	**9**	1.1 eq., 10 h	60%
6		**10**	2.0 eq., 4.5 h	68%

[a] Represents the equivalent of CsOH and reaction time. [b] Isolated yield of the mono-N-alkylated product. [c] Additionally, 15% trialkylamine was also obtained.

smoothly delivering the secondary amines in satisfactory yields, remarkably leaving the alcohol functionality intact (Table 5, entries 2 and 3). Moreover, amino esters such as valine methyl ester were efficiently converted, offering various monoalkylated products with use of three alkyl bromides (Table 5, entries 4−6). Above all, besides exceptional chemoselectivities, racemizations were not detected in any cases during the alkylation of these chiral templates, and complications stemming from hydrolysis or esterification were not observed.[25] Thus, these developed procedures are mild and efficient because side reactions commonly seen under basic conditions are averted.

Utilizing this methodology, issues of chemoselectivity were next examined by embarking on the synthesis of tripeptide mimics, which possess secondary amines in the skeletal backbone (Scheme 9). The synthesis of higher order peptidomometics such as trimer **44** was facile and expeditious by employing our cesium promoted N-alkylation technique.[24] As discussed above (Table 6), isoleucinol **39** was successfully coupled with amino bromide **33** to generate the corresponding protected dimer in its primary form. After debenzylation via hydrogenolysis, the free amine of dimer **42** was united with protected amino bromide **43** to afford trimer **44** cleanly, proceeding through aziridinium intermediate **45** (vide supra).[26] As mentioned in the above case, the primary amine reacted selectively leaving both the secondary amine and the

(23) Nagle, A. S.; Salvatore, R. N.; Chong, B. D.; Jung, K. W. *Tetrahedron Lett.* **2000**, *41*, 3011.

(24) Salvatore, R. N.; Schmidt, S. E.; Shin, S. I.; Nagle, A. S.; Worrell, J. H.; Jung, K. W. *Tetrahedron Lett.* **2000**, *41*, 9705.

(25) Optical rotations of the synthetic samples were compared with the known literature values. See: Bowman, W. R.; Coghlan, D. R. *Tetrahedron* **1997**, *53*, 15787. In addition, side reactions stemming from elimination were not observed within our detection limits in any case.

(26) ^1H NMR, ^{13}C NMR, and 2D NMR analysis indicate the product as a single diastereomer.

Scheme 9

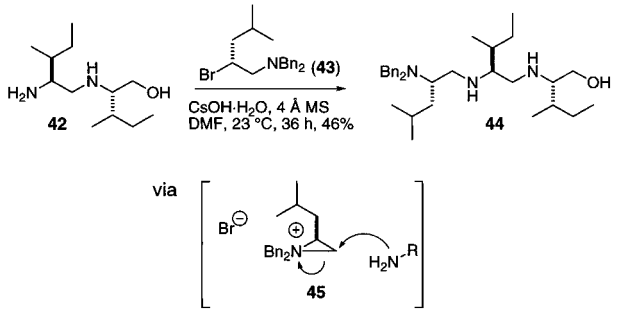
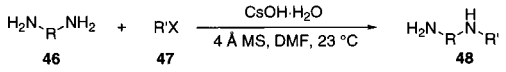
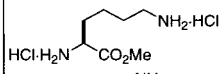
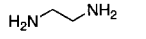
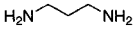
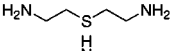
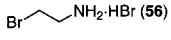
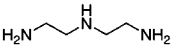
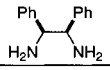


Table 7. CsOH-Promoted N-Alkylation of Diamines and Polyamines



entry	diamine or polyamine (**46**)	halide (**47**)	time	yield of **48**[a]
1	 (**49**)	**8**	28 h	77%
2	 (**50**)	BnCl (**51**)	12 h	70%[b]
3	 (**52**)	TsCl (**53**)	2 h	75%[c]
4	 (**54**)	**8**	24 h	65%
5	 (**55**)		12 h	73%
6	 (**57**)	**8**	24 h	58%
7	 (**58**)	**51**	12 h	79%

[a] Isolated yields of mono-N-alkylated amines. The starting amines were not consumed completely, accounting for the additional mass balance. [b] Overalkylation was minimized by performing the reaction at 0 °C. [c] The reaction was run using a catalytic amount of CsOH at 0 °C.

hydroxyl untouched, which illustrated the diminished reactivities of secondary amines and high chemoselectivity. These synthetic sequences may be practical in generating large compound libraries, which can be utilized in combinatorial screenings.

Diamines and Polyamines. After substantiating that our cesium-promoted conditions are indeed facile in promoting N- over O-alkylations, we then decided to augment our synthetic efforts toward the monofunctionalization of naturally occurring diamines and polyamines. Two shortcomings typically found in polyamine syntheses via the N-alkylation route are the employment of vulnerable nitrogen masking groups and virtually impossible selective functionalization of these naked biogenic amines.[27] Thus, these criteria prompted investigations on an efficient and selective N-alkylation protocol for bare diamines and polyamines.

Encouraged by high selectivities using unsymmetrical diamines, polyamines, and amino alcohols in our peptidomimetic synthesis, we recognized N-alkylations of other unsymmetrical diamines should be easily accessible. As representatively depicted in Table 7, various electrophiles as well as numerous diamines and polyamines were subjected to the proposed conditions to evaluate efficiency and chemoselectivity. Unsymmetrical diamine, 1,2-diaminopropane **49** also reacted regioselectively, alkylating exclusively at the primary carbon, leaving the amine at the secondary center untouched (Table 7, entry 1). Furthermore, chiral diamine L-lysine methyl ester **50** was selectively N-benzylated at the primary center, and no racemization was detected (Table 7, entry 2).[28]

Next, we turned our attention to the N-alkylation of symmetrical diamines. In the presence of a catalytic amount of CsOH (0.5 equiv), ethylenediamine **52** underwent N-tosylation to produce the protected diamine in high yield (Table 7, entry 3). In addition, bromide **8** reacted with symmetrical diamine **54** after 24 h (Table 7, entry 4). Also, NSN **55** underwent N-alkylation with 2-bromoethylamine·HBr **56** delivering the mono-N-alkylated product in 73% isolated yield, which is far superior to existing methods for the synthesis of this polyamine target molecule (Table 7, entry 5).[29] Similarly, polyamines encompassing diethylentriamine **57** (Table 7, entry 6) still proved pragmatic, exhibiting comparable selectivity as the starting diamine in Table 7, entry 4. This example illustrates the diminished reactivity of secondary amines embedded in the middle of alkyl chains, which is reminiscent of the peptidomimetic synthesis of the trimer analogue (*cf.* Scheme 9). Diamines containing elements of stereochemistry were also found to be compatible using our conditions. For example, a single benzyl unit was delivered to (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine **58** desymmetrizing the diamine (Table 7, entry 7), and overalkylation was not detected.

Cesium Carbonate as an Alternative. Although our synthetic efforts toward N-alkylation using CsOH proved most effective in terms of substrate compatibility and selectivity for generation of mono-N-alkylated products, it was decided to further expand on the preliminary results discussed in Scheme 6 using cesium carbonate. Coupled with the success of utilizing this base in our carbamations of amines,[30] Cs_2CO_3 is much easier to handle than its hydroxide counterpart due to its lower hygroscopicity. Therefore, the generality and limitations using this cesium base were next examined. As addressed in Table 8, methylamine·HCl **59**, which releases a very reactive primary amine, united with lipophilic lauryl bromide with the aid of TBAI to produce the surfactant *N*-methyldodecylamine in excellent yield (Table 8, entry 1). Under these conditions, methylbenzylamine **61** N-benzylated after 5 h in nearly quantitative yields (Table 8, entry 2). Since amine protection is of prime interest in organic synthesis, and for the most part, *N*-silyl derivatives are known not to provide satisfactory protection for primary amines due to their high sensitivity to moisture, an attempt was made to prepare secondary silylamines utilizing this methodology. With that in mind, benzylamine **22** was N-silylated, producing the TIPS analogue in 50% isolated yield after purification (Table 8, entry 3). Coming full circle, the initial substrates probed for this study were examined using 3 equiv of Cs_2CO_3, but gave a lower yield than CsOH (Table 8,

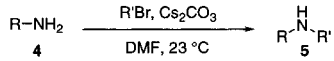
(27) Fiedler, W. J.; Hesse, M. *Helv. Chim. Acta* **1993**, *76*, 1511.

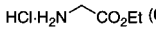
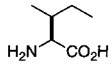
(28) The resulting product was converted back to the starting diamine (lysine methyl ester) by hydrogenolysis, followed by salt formation using dry HCl gas. The optical rotation of the resultant salt was 16.5°, whereas the reported value is 15.6° (c = 1.3; H_2O). See: Davies, C. E.; Heightman, T. D.; Hermitage, S. A.; Moloney, M. G. *Synth. Commun.* **1996**, *26*, 687.

(29) Tuemac, F. U. S. Patent 3,362,996, 1968; *Chem. Abstr.* **1968**, *68*, 77738.

(30) Salvatore, R. N.; Shin, S. I.; Nagle, A. S.; Jung, K. W. *J. Org. Chem.* **2001**, *66*, 1035.

Table 8. N-Alkylation of Primary Amines using Cs_2CO_3



entry	amine (RNH_2)		bromide(R'Br)	conditions	yield (**5**)
1	$MeNH_2$·HCl	(**59**)	lauryl bromide (**60**)	3 eq., 5 h, TBAI (3 eq.)	86%
2		(**61**)	**10**	1 eq., 5 h	97%
3	**22**		TIPSCl (**62**)	1.5 eq., 12 h	50%
4	**1**		**23**	3 eq., 24 h	71%
5	**41**		**10**	0.1 eq., 5h	50%
6		(**63**)	**10**	2 eq., 12h	51%
7		(**64**)	**10**	1 eq., 4 h	55%

entry 4). Switching focus, amino acid derivatives including valine methyl ester **41** and glycine ethyl ester **63** afforded similar yields upon reaction with benzyl bromide (Table 8, entries 5 and 6). It is noteworthy to mention that entry 5 (Table 8) required only a catalytic amount of cesium carbonate to carry out the desired transformation. Finally, an amino acid such as isoleucine **64** was found to undergo double alkylation, namely N-benzylation, along with the anticipated esterification. A cosolvent (10:1 DMF/H_2O) was used in order to enhance amino acid solubility (Table 8, entry 7). When CsOH was used for the same transformation, *N*,*N*-dibenzylamino esters were generated as the major products, indicating that cesium carbonate plays a complimentary role to cesium hydroxide in chemoselective N-alkylations.

Conclusion

In summary, we have established a cesium base-promoted N-alkylation methodology, which is more selective and efficient than other currently known methods. Since these enclosed reactions are fundamental in organic synthesis, our procedures can offer an attractive method for functionalizing alkylamines. High chemoselectivities involved in amine and polyamine alkylations have been clearly demonstrated, and use of protecting groups has been eliminated, offering a broad spectrum of possibilities. Various aliphatic amines including diamines and polyamines were compatible with reactive, unreactive, and secondary halides as well as a plethora of other electrophiles such as sulfonates. Furthermore, our procedures discussed herein were superior when compared to known methods since they averted overalkylations, offering mono-N-alkylated products predominantly or exclusively. In addition, these mild reaction conditions (ambient temperatures) and short reaction times enabled labile functionalities to be tolerated. Thus, chiral substrates including amino acids and their derivatives, which are easily prone to racemization, were also successfully transformed under the conditions, offering potential applications in peptidomimetic synthesis. This methodology proves to be a general protocol for the syntheses of various secondary amines, offering a wide variety of applications. Currently, efforts are underway to extend this procedure to the synthesis of aromatic secondary amines.

Experimental Section

General Methods. All experiments were carried out under a nitrogen atmosphere, using glassware, which was oven and/or flame-dried. Anhydrous *N*,*N*-dimethylformamide (99.8%) was purchased from Aldrich Chemical Co. All starting materials were obtained from commercial suppliers and used without further purification unless otherwise noted. Activated 4 Å molecular sieves were acquired from Aldrich Chemical Co. and were activated by heating at 120 °C for 24 h prior to use. Cesium bases were acquired from Acros, Aldrich, or Chemetall, Inc. Proton nuclear magnetic resonance (250 and 360 MHz) spectra and ^{13}C (90 MHz) were recorded at room temperature in $CDCl_3$, unless otherwise stated. All chemical shifts are reported as δ relative to $CHCl_3$ (δ_H 7.26 ppm) or $CDCl_3$ (δ_C 77.0 ppm) as internal standards, respectively, using a Brucker spectrometer. Optical rotations were measured at 25 °C using a Perkin-Elmer 241MC polarimeter set on the sodium D line. Infrared spectra were recorded using a Nicolet Magna FT IR 550 spectrometer and are reported in reciprocal centimeters (cm^{-1}). Elemental analyses were obtained by Atlantic Microlab, Inc., Norcross, GA.

General Procedure for N-Alkylation. To a suspension containing activated powdered 4 Å molecular sieves (500 mg) in anhydrous DMF (8.3 mL), cesium hydroxide monohydrate (280 mg, 1.7 mmol, 1 equiv) was added, and the mixture was vigorously stirred for 10 min. After **1** (0.21 mL, 1.7 mmol, 1 equiv) was added, the mixture was stirred for an additional 30 min. 1-Bromobutane (0.21 mL, 2.0 mmol, 1.2 equiv) was added to the white suspension, and the reaction was allowed to proceed at room temperature for 20 h. The reaction mixture was filtered to remove undissolved solids and washed several times with ethyl acetate. The filtrate was concentrated, and the residue was taken up in 1 N NaOH, and extracted with ethyl acetate (4 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The resulting crude mixture was purified by column chromatography using ethyl acetate–ethanol (9:1 v/v) as the eluting solvent to afford **2** (260 mg, 89%) as a colorless oil. Trialkylamine **3** (40 mg, 10%) was isolated as a pale yellow oil. Dialkylamine **2**: IR (film) 3290, 3063, 3027, 2956, 2872, 2815,1496, 1453, 1125, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 3 H), 1.25–1.35 (m, 2 H), 1.36–1.64 (m, 2 H), 1.75 (s, N*H*), 2.60 (t, J = 7.0 Hz, 2 H), 2.49–2.69 (m, 2 H), 2.77–2.92 (m, 2 H), 7.16–7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.78, 20.27, 31.82, 36.13, 49.33, 51.00, 125.88, 128.22, 128.47, 139.86. Trialkylamine **3**: IR (film) 3026, 2930, 2871, 2861, 2800, 1453, 1100, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89–0.98 (m, 6 H), 1.25–1.35 (m, 4 H), 1.40–1.53 (m, 4 H), 2.41–2.51 (m, 4 H), 2.67–2.75 (m, 4 H), 7.12–7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.08, 20.74, 29.29, 33.44, 53.80, 56.11, 125.80, 128.27, 128.69, 140.90.

Dialkylamine 6 (R′ = $PhCH_2CH_2CH_2$): 85% yield; IR (film) 3400, 3120, 3110, 2920, 2850 2800, 1490, 1150, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, N*H*), 1.76–1.85 (m, 2 H), 2.59–2.67 (m, 4 H), 2.78–2.93 (m, 4 H), 7.06–7.31 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 31.17, 32.57, 34.41, 46.32, 48.28, 123.7, 124.01, 126.15, 136.73, 139.20.

Trialkylamine 7 (R′ = $PhCH_2CH_2CH_2$): 10% yield; ^1H NMR ($CDCl_3$) δ 1.76–1.89 (m, 4 H), 2.56 (t, J = 7.1 Hz, 4 H), 2.65 (t, J = 7.8 Hz, 4 H), 2.73 (s, 4 H), 7.18–7.31 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 28.79, 33.39, 33.63, 53.33, 55.87, 125.64, 125.82, 128.23, 128.67, 140.68, 142.28.

N-Alkylation Using a Catalytic Amount of CsOH. Phenethylamine **1** (0.21 mL, 1.7 mmol, 1 equiv) was dissolved in anhydrous DMF (8.3 mL), and activated 4 Å molecular sieves (500 mg) and cesium hydroxide monohydrate (28 mg, 0.165 mmol, 0.1 equiv) were added to the mixture and stirred for 30 min at room temperature. Allyl bromide (0.17 mL, 2.0 mmol, 1.2 equiv) was added in one portion to the white suspension, and the reaction was allowed to proceed for 4.5 h. The suspension was then filtered and rinsed with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was taken up in 1 N NaOH and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with water (2 × 30 mL) and brine (30 mL) and dried using anhydrous sodium sulfate. Concentration of the solvent and purification by flash column chromatography (9:1 EtOAc/EtOH) yielded the desired dialkylamine **6** (220 mg, 85%) as a clear oil and the trialkylamine **7** (50 mg, 15%) as a yellow oil. Dialkylamine **6** (R = allyl): IR

(film) 3313, 3077, 3063, 2956, 2924, 2854, 2816,1495, 1453, 918, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (s, N*H*), 2.82−2.91 (m, 4 H), 3.27 (d, J = 6.5 Hz, 2 H), 5.13 (m, 2 H), 5.88 (ddt, J = 17, 10.3, 6 Hz, 1 H), 7.18−7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 36.13, 50.32, 52.11, 116.19, 126.13, 128.25, 136.25, 139.80. Trialkylamine **7** (R, R′ = allyl): 15% yield; ^1H NMR ($CDCl_3$) δ 2.72−2.80 (m, 4 H), 3.20 (d, J = 6.4 Hz, 4 H), 5.16 (m, 4 H), 5.86 (ddt, J = 17.1, 10.4, 6 Hz, 2 H), 7.17−7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 33.11, 55.00, 56.71, 117.55, 125.85, 128.25, 128.64, 135.41, 140.43.

Dialkylamine 6 (R′ = Bn): 85% yield; IR (film) 3350, 3026, 2925, 2872, 2815, 1497, 1455, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (s, N*H*), 2.72−2.92 (m, 4 H), 3.79 (s, 2 H), 7.07−7.49 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 36.10, 50.33, 53.63, 126.10, 126.94, 128.10, 128.33, 128.39, 128.65, 139.80.

Trialkylamine 7 (R′ = Bn): 15% yield; ^1H NMR ($CDCl_3$) δ 2.59−2.61 (m, 4 H), 3.52 (s, 4 H), 6.94−7.21 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 33.26, 54.88, 57.98, 125.67, 126.69, 128.03, 128.19, 128.55, 128.66, 128.84, 139.9, 140.0.

Dialkylamine 6 (R′ = $CH_3CH(CH_3)CH_2$): 74% yield; ^1H NMR ($CDCl_3$) δ 0.81 (d, J = 6.5 Hz, 6 H), 1.22 (s, N*H*), 1.60−1.71 (m, 1 H), 2.36 (d, J = 6.7 Hz, 2 H), 2.73−2.79 (m, 4 H), 6.99−7.24 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 20.48, 28.08, 36.22, 51.14, 57.69, 125.90, 128.24, 128.57, 139.98.

CsOH-Promoted N-Alkylation Using Secondary Bromides. Activated 4 Å molecular sieves (500 mg) and cesium hydroxide monohydrate (856 mg, 5.1 mmol, 3.0 equiv) were added to a solution of phenethylamine **1** (0.21 mL, 1.7 mmol, 1 equiv) in anhydrous DMF (8.3 mL), and the mixture was stirred for 30 min at room temperature. 2-Bromobutane (0.9 mL, 8.2 mmol, 5.0 equiv) was added in one portion to the white suspension, and the reaction was allowed to proceed for 48 h. The mixture was then filtered and rinsed with ethyl acetate. The filtrate was concentrated, and then the residue was taken up in 1 N NaOH and extracted with ethyl acetate (3 × 30 mL). The organic layers were washed with water (2 × 30 mL) and brine (30 mL) and dried over anhydrous sodium sulfate. Concentration of the solvent and purification by flash column chromatography (9:1 EtOAc/EtOH) afforded the desired dialkylamine **6** (230 mg, 80%) as a clear oil. The trialkylamine **7** was not observed. Dialkylamine **6** (R′ = $CH(CH_3)CH_2CH_3$): IR (film) 3306, 3084, 3061, 3025, 2931, 2855, 2810, 1495, 1457, 1125, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, J = 7.5 Hz, 3 H), 1.00 (d, J = 6.1 Hz, 3 H), 1.24−1.31 (m, 2 H), 2.78−2.89 (m, 5 H), 7.12−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 10.00, 19.54, 29.28, 35.35, 48.35, 54.21, 125.89, 128.21, 128.45, 139.91.

Dialkylamine 6 (R′ = $CH(CH_3)_2$): 70% yield; ^1H NMR ($CDCl_3$) δ 1.09 (d, J = 8.2 Hz, 6 H), 1.54 (s, N*H*), 2.62−2.89 (m, 5 H), 7.21−7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 22.72, 36.37, 48.49, 48.65, 126.03, 128.58, 139.93. Anal. Calcd for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.58. Found: C, 80.72; H, 10.40; N, 8.26.

CsOH-Promoted N-Alkylation Using Alkyl Sulfonates (15a). Into a stirred solution of phenethylamine **1** (75 mg, 0.62 mmol, 1 equiv) in anhydrous DMF (4 mL) were added activated 4 Å molecular sieves (500 mg) and cesium hydroxide monohydrate (100 mg, 0.62 mmol, 1 equiv). The white mixture was then stirred for 30 min at room temperature. A solution of 3-phenyl-1-propyl tosylate (220 mg, 0.75 mmol, 1.2 equiv) in DMF was added dropwise, and the reaction was allowed to proceed at the same temperature for 22 h. The reaction mixture was then filtered and continually rinsed with ethyl acetate. The filtrate was concentrated, and then the residue was taken up in 1 N NaOH and extracted with ethyl acetate (3 × 30 mL). The organic layers were washed with water (2 × 30 mL) and brine (30 mL) and dried over anhydrous sodium sulfate. The solvent was concentrated in vacuo, and the residue was purified by flash column chromatography (9:1 EtOAc/EtOH) to afford the desired dialkylamine **6** (74 mg, 50%) as a colorless oil.

Compound 15b. After phenethylamine **1** (0.15 mL, 1.2 mmol, 1 equiv) was dissolved in anhydrous DMF (6 mL), 4 Å activated molecular sieves (500 mg) and powered cesium hydroxide monohydrate (200 mg, 1.2 mmol, 1 equiv) were added consecutively and the suspension was vigorously stirred for 30 min under inert atmosphere. A solution of 3-phenyl-1-propyl mesylate (308 mg, 1.5 mmol, 1.44 equiv) dissolved in DMF was added dropwise, and the reaction was stirred for 22 h at ambient temperature. The mixture was filtered to remove undissolved sieves and inorganic salts and rinsed with ethyl acetate. The filtrate was evaporated, and the residue was taken up in 1 N NaOH and extracted with ethyl acetate (3 × 30 mL). The resulting organic layer was washed consecutively with water (2 × 30 mL) and brine (30 mL) and dried using anhydrous sodium sulfate. Solvent was removed in vacuo, and the residue was subjected to flash column chromatography (9:1 EtOAc/EtOH), affording the desired dialkylamine **15b** (173 mg, 60%) as a colorless oil.

Compound 18: 56% yield; ^1H NMR ($CDCl_3$) δ 1.77 (s, N*H*), 2.20 (dd, J = 7.2, 3.4 Hz, 1 H), 2.50 (dd, J = 7.5, 4.5 Hz, 1 H), 3.50−3.55 (m, 1 H), 3.65 (m, 2 H), 3.94 (dd, J = 7.5, 3.7 Hz, 1 H), 4.21 (dd, J = 7.5, 5.7 Hz, 1 H), 7.15−7.21 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 35.37, 51.32, 53.46, 73.10, 127.46, 127.69, 128.52, 139.09, 176.09.

General Procedure for One-Pot N-Alkylation Using Cs_2CO_3. γ-Butyrolactone **16** (0.16 mL, 1.94 mmol, 1 equiv), was dissolved in dry methylene chloride (10 mL), the mixture was cooled to 0 °C, and dry triethylamine (0.33 mL, 2.2 mmol, 1.2 equiv) was added. Methanesulfonyl chloride (0.17 mL, 2.2 mmol, 1.2 equiv) was added dropwise, and the mixture was warmed to room temperature and allowed to stir for 2 h. Upon consumption of starting material (alcohol), the solvent was evaporated and the crude mixture was taken up in anhydrous DMF (10 mL). Benzylamine (0.21 mL, 1.94 mmol, 1 equiv) was added, followed by a catalytic amount of powered cesium carbonate (50 mg), and the reaction was stirred at room temperature for 24 h. The reaction was quenched with water, and the aqueous phase was extracted with ethyl acetate (4 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give pale yellow oil. The resulting crude mixture was purified by column chromatography using hexanes/ethyl acetate (1:1 v/v) to afford the dialkylamine **18** (246 mg, 56%) as a pale yellow oil.

Dialkylamine 5 (R = Bn, R′ = Bu): 83% yeild; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.4 Hz, 3 H), 1.25−1.35 (m, 2 H), 1.36−1.52 (m, 4 H), 1.75 (s, N*H*), 2.62 (t, J = 7.0 Hz, 2 H), 3.78 (s, 2 H), 7.23−7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.5, 34.4, 48.8, 55.0, 29.56, 126.8, 128.1, 128.8, 137.2. Anal. Calcd for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.58. Found: C, 79.90; H, 10.39; N, 8.37.

Trialkylamine 21 (R = Bn, R′ = Bu): 10% yield; ^1H NMR ($CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 6 H), 1.33−1.39 (m, 4 H), 1.39 (m, 4 H), 2.36 (t, J = 7.0 Hz, 4 H), 3.62 (s, 2 H), 7.06−7.14 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 20.8, 32.2, 53.5, 59.7, 127.0, 128.2, 129.0, 136.3.

Dialkylamine 5 (R = Bn, R′ = octyl): 75% yield; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3 H), 1.26−1.31 (m, 10 H), 1.47−1.52 (m, 2 H), 2.25 (s, N*H*), 2.60 (t, J = 7.2 Hz, 2 H), 3.77 (s, 2 H), 7.20−7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.04, 22.59, 27.25, 29.19, 29.41, 29.56, 31.76, 49.06, 53.61, 127.10, 128.33, 128.40, 139.25.

Trialkylamine 21 (R = Bn, R′ = octyl): 13% yield; ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 6.8 Hz, 6 H), 1.25−1.31 (m, 20 H), 1.43−1.47 (m, 4 H), 2.38 (t, J = 7.2 Hz, 4 H), 3.53 (s, 2 H), 7.21−7.33 (m, 5 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.07, 22.65, 27.01, 27.42, 29.32, 29.53, 31.86, 53.79, 58.63, 126.49, 127.95, 128.06, 128.29, 128.74, 140.24.

Dialkylamine 5 (R = octyl, R′ = $(CH_2)_3Ph$): 80% yield; IR (film) 3250, 3050, 3025, 3000, 2950, 2850, 2780, 1480, 1110, 750; ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 6.8 Hz, 3 H), 1.20−1.35 (m, 8 H), 1.40−1.50 (m, 2 H), 1.78−1.80 (m, 4 H), 3.50−3.70 (m, 6 H), 7.10−7.28 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.96, 22.52, 27.40, 29.29, 29.39, 29.54, 31.62, 33.56, 40.20, 49.06, 53.61, 126.58, 128.15, 128.31, 141.34. Anal. Calcd for $C_{17}H_{29}N$: C, 82.48; H, 11.81; N, 5.66. Found: C, 81.49; H, 11.66; N, 5.54.

Trialkylamine 21 (R = octyl, R′ = $(CH_2)_3Ph$): 10% yield; ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3 H), 1.29 (m, 12 H), 1.90 (t, J = 6.4 Hz, 4 H), 2.40−2.49 (m, 6 H), 2.60−2.71 (m, 4 H), 7.16−7.30 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 14.04, 22.60, 27.30, 28.10, 29.19, 29.56, 30.11, 31.55, 37.89, 53.61, 54.12,

127.15, 128.33, 128.41, 139.30. Anal. Calcd for $C_{26}H_{39}N$: C, 83.41; H, 10.75; N, 3.83. Found: C, 83.29; H, 10.39; N, 3.60.

Dialkylamine 5 (R = cyclohexylmethyl, R′ = $(CH_2)_3Ph$): 90% yield; IR (film) 3320, 3084, 3062, 3025, 2850, 2807,1495, 1457, 1128, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80−0.90 (m, 2 H), 1.18−1.26 (m, 4 H), 1.39−1.51 (m, 1 H), 1.68−1.82 (m, 6 H), 2.40 (d, J = 6.8 Hz, 2 H), 2.58−2.65 (m, 4 H), 7.10−7.28 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 24.67, 24.82, 29.72, 29.87, 31.68, 36.10, 47.82, 123.84, 126.32, 126.47, 140.32.

Trialkylamine 21 (R = cyclohexylmethyl, R′ = $(CH_2)_3Ph$): 10% yield; ^1H NMR ($CDCl_3$) δ 0.85−0.87 (m, 2 H), 1.23 (m, 4 H), 1.40−1.45 (m, 1 H), 1.73−1.83 (m, 8 H), 2.18 (d, J = 3.8 Hz, 2 H), 2.44 (s, 4 H), 2.65 (s, 4 H), 7.18−7.30 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 26.10, 26.80, 28.88, 31.87, 32.79, 33.57, 36.07, 54.10, 61.61, 125.48, 128.26, 128.37, 142.42.

Dialkylamine 5 (R = cyclopropyl, R′ = $(CH_2)_3Ph$): 83% yield; ^1H NMR ($CDCl_3$) δ 0.56−0.64 (m, 4 H), 2.03−2.05 (m, 2 H), 2.26−2.31 (m, 1 H), 2.73 (t, J = 7.7 Hz, 2 H), 2.88 (t, J = 7.2 Hz, 2 H) 4.35 (s, N*H*), 7.25−7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 4.17, 28.11, 30.29, 32.89, 48.37, 126.03, 128.20, 128.35, 140.31.

Trialkylamine 21 (R = cyclopropyl, R′ = $(CH_2)_3Ph$): 12% yield; ^1H NMR ($CDCl_3$) δ 0.56−0.59 (m, 4 H), 1.80−1.86 (m, 1 H), 1.96 (d, J = 2.3 Hz, 4 H), 2.70−2.78 (m, 8 H), 7.09−7.53 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 6.75, 28.51, 33.83, 36.53, 54.89, 125.55, 128.16, 128.25, 142.37.

Dialkylamine 5 (R = cyclooctyl, R =$(CH_2)_3Ph$): 75% yield; ^1H NMR ($CDCl_3$) δ 1.27−1.86 (m, 17 H), 2.61−2.65 (m, 5 H), 7.17−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 24.00, 25.61, 27.10, 31.78, 32.52, 33.63, 46.86, 57.78, 125.55, 128.12, 128.17, 141.96.

Trialkylamine 21 (R = cyclooctyl, R′ = $(CH_2)_3Ph$): 10% yield; ^1H NMR ($CDCl_3$) δ 1.26−1.89 (m, 22 H), 2.54−2.64 (m, 5 H), 7.21−7.33 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 23.95, 25.57, 27.06, 31.73, 32.48, 33.59, 46.81, 57.74, 125.50, 128.07, 128.13, 141.92.

Dialkylamine 5 (R = adamantyl, R′ = $(CH_2)_3Ph$): 82% yield; IR (film) 3350**,** 3061, 3024, 2910, 2847, 2769, 1497, 1451, 1197, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57−1.72 (m, 15 H), 1.81−1.90 (m, 2 H), 2.10 (s, N*H*), 2.62−2.68 (m, 4 H), 7.16−7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 29.29, 29.58, 32.14, 33.83, 36.67, 39.86, 41.99, 42.28, 51.48, 125.83, 128.29, 128.44, 141.86.

Dialkylamine 5 (R = adamantyl, R′ = cinnamyl): 66% yield; IR (film) 3310, 3050, 3024, 3000, 2910, 2847, 1650, 1448, 968, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58−1.75 (m, 15 H), 2.50 (s, N*H*), 3.44 (d, J = 7.9 Hz, 2 H), 6.35 (dt, J = 16.8, 7.4 Hz, 1 H), 6.53 (d, J = 16.8 Hz, 1 H), 7.19−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 29.42, 36.47, 42.16, 42.88, 51.46, 126.19, 127.21, 128.38, 131.36, 136.99.

Dialkylamine 5 (R = *t*-Bu, R′ = $(CH_2)_3Ph$): 90% yield; IR (film) 3300, 3062, 3026, 2933, 2859, 2824, 2815, 1496, 1453, 1232, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 9 H), 1.78−1.83 (m, 2 H), 2.05 (s, N*H*), 2.56−2.64 (m, 4 H), 7.14−7.25 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 28.73, 32.26, 33.63, 41.88, 50.31, 125.53, 128.09, 128.17, 141.92. Anal. Calcd for $C_{13}H_{21}N$: C, 76.61; H, 10.06; N, 6.32. Found: C, 75.36; H, 10.13; N, 6.38.

Dialkylamine 5 (R = *tert*-octyl, R′ = Bn): 87% yield; ^1H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 1.17 (s, 6 H), 1.45 (s, 2 H), 3.68 (s, 2 H), 7.04−7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 29.04, 31.72, 46.57, 53.01, 54.44, 126.53, 128.07, 128.24, 141.57. Anal. Calcd for $C_{15}H_{25}N$: C, 81.75; H, 11.49; N, 6.35. Found: C, 81.94; H, 11.44; N, 6.26.

Dialkylamine 5 (R = octyl, R′ = Bu): 93% yield; ^1H NMR ($CDCl_3$) δ 0.86−0.91(m, 6 H), 1.25 (m, 12 H), 1.39 (m, 4 H), 2.35−2.39 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.06, 20.77, 22.63, 26.96, 27.63, 29.14, 29.29, 29.57, 31.83, 53.90, 54.21. Anal. Calcd for $C_{12}H_{27}N$: C, 78.76; H, 14.68; N, 5.56. Found: C, 79.46; H, 14.45; N, 5.72.

Dialkylamine 34: 54% yield; ^1H NMR ($CDCl_3$) δ 0.87−0.92 (m, 6 H), 1.17−1.21 (m, 1 H), 1.43−1.47 (m, 1 H), 1.88 (m, 1 H), 2.57 (d, J = 8.5 Hz, 2 H), 2.66−2.79 (m, 5 H), 2.8 (s, N*H*), 2.97−3.46 (*AB*, J_{AB} = 13.4 Hz, 2 H), 3.74−3.78 (A*B*, J_{AB} = 13.7 Hz, 2 H), 7.12−7.41 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 12.13, 16.43, 29.07, 32.52, 36.48, 47.31, 51.25, 54.36, 60.95, 126.41, 127.03, 128.42, 128.63, 129.09, 140.25, 140.40.

Dialkylamine 36: 45% yield; ^1H NMR ($CDCl_3$) δ 2.10 (s, N*H*), 2.34−2.64 (m, 8 H), 2.92−3.10 (m, 1 H), 3.39 (*AB*, J_{AB} = 13.4 Hz, 2 H), 3.73 (A*B*, J_{AB} = 13.4 Hz, 2 H), 7.05−7.30 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 34.23, 38.44, 49.66, 51.29, 53.63, 59.46, 124.35, 125.00, 126.99, 128.38, 128.77, 129.05, 139.50.

Dialkylamine 5 (R = 2-methoxyethyl, R′ =$(CH_2)_3Ph$): 84% yield; ^1H NMR ($CDCl_3$) δ 1.84−1.90 (m, 2 H), 2.63−2.70 (m, 4 H), 2.80 (t, J = 5.1 Hz, 2 H), 3.12 (s, N*H*), 3.34 (s, 3 H), 3.50 (t, J = 5.0 Hz, 2 H), 7.12−7.33 (m, 5 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 30.93, 33.30, 48.79, 48.99, 58.63, 71.17, 125.68, 128.21, 141.66.

Trialkylamine 21 (R = 2-methoxyethyl, R′ = $(CH_2)_3Ph$): 15% yield; IR (film) 3084,3062, 2939, 2861, 2811, 1496, 1453, 1117, 1079, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77−1.85 (m, 4 H), 2.53−2.57 (m, 4 H), 2.63−2.70 (m, 6 H), 3.33 (s, 3 H), 3.40 (t, J = 6.2 Hz, 2 H), 7.17−7.37 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 28.65, 33.57, 53.34, 54.07, 58.67, 71.12, 125.70, 128.17, 128.28, 142.25.

Dialkylamine 5 (R = valine, R′ = Bn): 74% yield; IR (film) 3348, 3104, 3072, 3032, 2960, 2868, 1472, 1038, 709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 1.84−1.89 (m, 1 H), 2.44−2.45 (m, 3 H), 3.37 (dd, J = 17.0, 7.2 Hz, 1 H), 3.62 (dd, J = 17.0, 7.2 Hz, 1 H), 3.72−3.81 (m, 2 H), 7.09−7.31 (m, 5 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.39, 19.55, 28.79, 51.32, 60.35, 63.82, 127.10, 128.12, 128.46.

Dialkylamine 5 (R = isoleucine, R′ = Ile-NBn_2): 52% yield; ^1H NMR ($CDCl_3$) δ 0.86−0.93 (m, 12 H), 1.17−1.19 (m, 2 H), 1.41 (m, 1 H), 1.51−1.54 (m, 2 H), 2.15 (s, 2 H), 2.40−2.47 (m, 2 H), 2.70−2.76 (m, 2 H), 3.30 (m, 1 H), 3.44 (*AB*, J_{AB} = 13.5 Hz, 2 H), 3.50−3.53 (m, 1 H), 3.73 (A*B*, J_{AB} = 13.5 Hz, 2 H), 7.23−7.37 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 11.48, 15.92, 16.32, 26.78, 32.77, 46.00, 54.02, 54.48, 58.32, 59.17, 62.84, 127.09, 128.14, 128.95, 139.7.

Dialkylamine 5 (R = valine methyl ester, R′ = 5-pentenyl): 65% yield; $[\alpha]^{25}_D$ = −10.0 (lit.[25] $[\alpha]^{25}_D$ = −9.9 (*c* = 1.8 in $CHCl_3$)); IR (film) 3355, 3085, 2973, 2933, 1742, 1643, 1472, 1183, 992, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 1.5−1.64 (m, 2 H), 1.62 (s, 1 H), 1.93 (m, 1 H), 2.13 (m, 2 H), 2.41 (m, 1 H), 2.61 (m, 1 H), 2.95 (d, J = 6.1, 1 H), 3.70 (s, 3 H), 4.95 (dd, J = 10.2, 1.3 Hz, 1 H), 5.01 (m, 1 H), 5.80 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.81, 19.15, 29.33, 31.38, 31.65, 48.12, 51.35, 67.48, 114.30, 138.50, 175.90.

Dialkylamine 5 (R = valine methyl ester, R′ = allyl): 60% yield; ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 1.55 (m, N*H*), 1.83 (m, 1H), 3.02−3.06 (m, 2 H), 3.26 (m, 1 H), 3.65 (s, 3 H), 4.97 (m, 1 H), 5.12 (m, 1 H), 5.80 (ddt, J = 17.0, 10.4, 6.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.35, 19.21, 31.34, 50.21, 51.03, 66.05, 115.84, 136.31, 156.03, 175.38.

Dialkylamine 5 (R = valine methyl ester, R′ = Bn): 60% yield; $[\alpha]^{25}_D$ = −49.5 (lit.[25] $[\alpha]^{25}_D$ = −50.2 (*c* = 1.0 in MeOH)); ^1H NMR ($CDCl_3$) δ 0.94 (d, J = 6.8 Hz, 6 H), 1.77 (s, N*H*), 1.89−1.94 (m, 1 H), 3.01 (d, J = 6.1 Hz, 1 H), 3.58 (*AB*, J_{AB} = 12.5 Hz, 1 H), 3.71 (s, 3 H), 3.82 (A*B*, J_{AB} = 12.5 Hz, 1 H), 7.23−7.7.3 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 18.54, 19.20, 31.59, 51.26, 52.43, 66.44, 126.86, 128.13, 128.16, 139.97, 175.65. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.23; H, 8.70; N, 6.35.

Dimer 42: 52% yield; ^1H NMR ($CDCl_3$) δ 0.74−0.86 (m, 12 H), 1.22−1.52 (m, 5 H), 1.73−1.85 (m, 2 H), 2.87−2.93 (m, 2 H), 3.34 (m, 1 H), 3.71−3.73 (m, 1 H), 3.80−3.83 (m, 1 H), 6.88 (br s, 4 H).

Trimer 44: 46% yield; ^1H NMR ($CDCl_3$) δ 0.70−0.93 (m, 12 H), 1.07 (s, 6 H), 1.29−1.42 (m, 8 H), 2.45−2.51 (m, 1 H), 2.73−2.76 (m, 1 H), 3.19 (s, 3 H), 3.39−3.47 (m, 6 H), 3.86 (*AB*, J = 13.5 Hz, 2 H), 4.00 (A*B*, J = 13.4 Hz, 2 H), 7.08−7.38 (m, 10 H).

Diamine 48 (R = 1,2-diaminopropane, R′ = $(CH_2)_3Ph$): 77% yield; ^1H NMR (D_2O) δ 0.96 (m, 3 H), 1.68 (m, 2 H), 2.36−2.45 (m, 6 H), 3.00 (m, 1 H), 7.06−7.17 (m, 5 H); ^{13}C NMR (D_2O) 21.49, 32.45, 35.36, 48.05, 50.77, 56.44, 128.28, 130.87, 144.58.

Diamine 48 (R = L-lysine methyl ester, R′ = Bn): 70% yield; ^1H NMR ($CHCl_3$) δ 1.49 (m, 2 H), 1.56 (m, 2 H), 1.58 (m, 2 H), 2.42 (m, 2 H), 3.55 (m, 1 H), 3.60 (s, 2 H), 3.80 (s, 3 H), 7.24−7.39 (m, 5 H); ^{13}C NMR ($CHCl_3$) 23.43, 26.74, 34.78, 51.84,

58.23, 60.61, 126.7, 128.1, 139.8, 176.0. The resulting product was converted back to the starting diamine (lysine methyl ester) by hydrogenolysis, followed by salt formation using dry HCl gas. The optical rotation of the resultant salt was 16.5°, whereas the reported value is 15.6° (c = 1.3; H_2O).[28]

Diamine 48 (R = ethylenediamine, R′ = Ts): 75% yield; ^{1}H NMR (D_2O) δ 2.41 (s, 3 H), 2.78 (t, J = 6.23 Hz, 2 H), 2.97 (t, J = 6.23 Hz, 2 H) 7.42 (d, J = 7.8 Hz, 2 H), 7.72 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (D_2O) δ 23.04, 42.27, 45.90, 129.07, 132.44.

Diamine 48 (R = 1,3 propanediamine, R′ = $(CH_2)_3$Ph): 65% yield; ^{1}H NMR (D_2O) δ 2.00 (m, 4 H), 2.72 (m, 2 H), 3.04 (m, 6 H) 7.29−7.36 (m, 5 H); ^{13}C NMR (D_2O) 21.49, 32.45, 35.36, 48.05, 50.77, 56.44, 128.28, 130.87, 144.58.

Diamine 48 (NNSN): 73% yield; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.46 (br s, 5 H, N*H*) 2.62 (2 H), 2.67 (2 H), 2.75 (2 H), 2.79 (2 H), 2.81 (t, J = 6.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$**)** 32.1, 36.1, 41.1, 41.6, 48.5, 52.0, 58.23.

Polyamine 48 (R = diethylenetriamine, R′ = $(CH_2)_3$Ph): 58% yield; ^{1}H NMR (D_2O) δ 1.98 (m, 2 H), 2.22−3.05 (m, 12 H), 7.03−7.34 (m, 5 H); ^{13}C NMR (D_2O) 29.59, 34.28, 46.57, 49.17, 49.40, 128.9, 130.9, 131.2, 143.1.

Diamine 48 (R = diphenyldiamine, R′ = Bn): 79% yield; ^{1}H NMR (D_2O) δ 1.75 (m, 1 H), 3.05 (m, 1 H), 4.34 (s, 2 H), 3.04 (m, 6 H) 7.21−7.41 (m, 15 H); ^{13}C NMR (D_2O) 52.4, 60.8, 66.1, 126.5, 128.1, 137.2, 142.4.

Dialkylamine 5 (R = Me, R′ = lauryl): 86% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 6.8 Hz, 3 H), 1.25 (m, 23 H), 1.40 (m, 2 H), 2.19 (s, N*H*), 2.29 (J = 7.56 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 23.1, 27.7, 30.0, 32.0.

N-Alkylation of 61 Using Cs_2CO_3. Into a stirred solution of DL-methylbenzylamine **61** (200 mg, 1.65 mmol, 1 equiv) in anhydrous DMF (8.3 mL) was added powdered cesium carbonate (540 mg, 1.65 mmol, 1 equiv). The mixture was stirred at ambient temperature for 30 min. Benzyl bromide (0.24 mL, 2.0 mmol, 1.2 equiv) was added dropwise with efficient stirring, and the reaction was allowed to proceed for 5 h at room temperature. The reaction mixture was then filtered to remove undissolved inorganic salts and continually washed with ethyl acetate. The filtrate was concentrated, and the residue was taken up in 1 N NaOH and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with water (2 × 30 mL) and brine (30 mL) and dried over anhydrous sodium sulfate. The solvent was concentrated in vacuo, and the residue was purified by flash column chromatography (9:1 EtOAc/EtOH) to afford the desired dialkylamine **5** (340 mg, 97%) as an oil and the trialkylamine **21** (15 mg, 3%). Dialkylamine **5** (R = α-methylbenzyl, R′ = Bn): ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J = 6.5 Hz, 3 H), 1.71 (s, N*H*), 3.55 (*A*B, J_{AB} = 14.4 Hz, 1 H), 3.62 (A*B*, J_{AB} = 14.4 Hz, 1 H), 3.77 (q, J = 6.5 Hz, 1 H), 7.15−7.32 (m, 10 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 24.40, 51.86, 57.41, 126.62, 126.77, 126.86, 128.06, 128.28, 128.39. Trialkylamine **21** (R = α-methylbenzyl, R′ = Bn): ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 6.8 Hz, 3 H), 3.37 (*A*B, J_{AB} = 13.8 Hz, 2 H), 3.52 (A*B*, J_{AB} = 13.8 Hz, 2 H), 3.80−3.86 (q, J = 6.8 Hz, 1 H) 7.01−7.31 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 13.73, 53.54, 56.13, 126.70, 127.93, 128.00, 128.16, 128.62, 140.42, 142.71.

N-Alkylation of 1 with TIPSCl. Powdered cesium carbonate (920 mg, 2.8 mmol, 1.5 equiv) was added to anhydrous DMF (9.5 mL). Benzylamine **22** (0.5 mL, 1.86 mmol, 1 equiv) was injected 10 min later into the turbid solution, which was stirred for an additional 30 min. Triisopropylsilyl chloride (0.40 mL, 2.05 mmol, 1.1 equiv) was added, and the reaction was allowed to proceed at room-temperature overnight. The reaction was then filtered to remove undissolved solids and washed with ethyl acetate. The filtrate was washed with water (3 × 30 mL), and the organic layer was washed with brine (30 mL) and dried using anhydrous sodium sulfate. Solvent was removed in vacuo, and the residue was purified via flash column chromatography (5:1 hexanes/EtOAc) to yield the desired silyl protected dialkylamine **5** (200 mg, 50%) as a clear yellow oil. Dialkylamine **5** (R = Bn, R′ = TIPS): 50% yield; ^{1}H NMR ($CDCl_3$) δ 0.89−0.90 (m, 21 H), 2.90 (s, N*H*), 4.25 (s, 2 H), 7.10−7.25 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 12.23, 17.61, 41.93, 126.81, 126.97, 127.60, 128.54.

Dialkylamine 5 (R = glycine ethyl ester, R′ = Bn): 51% yield; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 12.0 Hz, 3 H), 1.90 (s, N*H*), 3.28 (s, 2 H), 3.75 (s, 2 H), 4.09 (q, J = 9.6 Hz, 2 H), 7.15−7.35 (m, 5 H).

N-Alkylation of 64 Using Cs_2CO_3. Cesium carbonate (487 mg, 1.5 mmol, 1 equiv) was dissolved in DMF (8 mL) and distilled water (0.8 mL) (10:1 v/v). L-Isoleucine **64** (196 mg, 1.5 mmol, 1 equiv) was added, and the mixture was stirred for 30 min. By syringe, benzyl bromide (0.36 mL, 3.0 mmol, 2 equiv) was added to the white suspension, and the reaction was allowed to proceed at room temperature for an additional 3.5 h. The mixture was then filtered to remove undissolved solids, and washed several times with ethyl acetate. After the filtrate was concentrated, the residue was purified by column chromatography using hexanes/ethyl acetate (5:1 v/v) to afford amino ester **5** (256 mg, 55%) as a colorless oil. Dialkylamine **5** (R = isoleucine benzyl ester, R′ = Bn): 55% yield; ^{1}H NMR ($CDCl_3$) δ 0.81−0.96 (m, 6 H), 1.23−1.29 (m, 1 H), 1.60−1.64 (m, 1 H), 1.64−1.78 (m, 1 H), 1.88 (s, N*H*), 3.20 (d, J = 6.2 Hz, 1 H), 3.64 (*A*B, J_{AB} = 12.9 Hz, 1 H), 3.87 (A*B*, J_{AB} = 12.9 Hz, 1 H), 5.22 (s, 2 H), 7.25−7.43 (m, 10 H).

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Supporting Information Available: Copies of the spectral data for all the compounds in the schemes and tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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