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Ring opening of aziridines with *ortho*-bromophenyl metal reagents: synthesis of 2-substituted indolines

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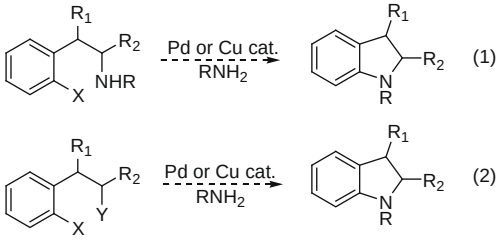
ABSTRACT

Stabilized *ortho*-bromo phenyllithium reagents, generated via lithium-halogen exchange of aryl iodides, undergo regioselective ring opening of mono-substituted *N*-Boc, *N*-Cbz, and *N*-tosyl-protected aziridines in good to excellent yields. The resulting *ortho*-bromo phenethylamines can be cyclized under transition-metal-catalyzed conditions to give 2-substituted chiral, non-racemic indolines in good yields.

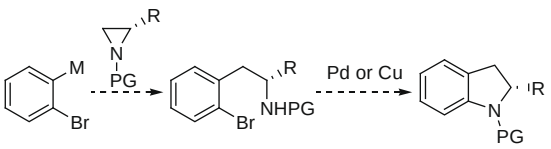
Indolines are important structures that can be found in a number of natural and synthetic biologically active compounds as well as ligands in transition-metal-catalyzed reactions.[1] A number of elegant and useful approaches toward the synthesis of indolines have been developed, including transition-metal-catalyzed intramolecular amination and amidation reactions of *ortho*-halo phenethylamines (Scheme 1, Eq. 1).[2] In addition, domino processes involving one-pot amination/N-alkylation reactions (Scheme 1, Eq. 2) have been reported.[3] A number of these latter approaches require the use of specific N-protecting groups or alkyl electrophiles, and the starting materials for these reactions can require several steps to prepare.[4] As a result, the substrate scope of these processes is limited.

We were interested in preparing a number of indolines via intramolecular aryl amination/amidation (as in Scheme 1, Eq. 1) of *ortho*-halo phenethylamines. While this reaction is well precedented, the synthesis of the starting phenethylamines can be quite complicated, especially with compounds bearing more elaborate aryl rings. We envisioned that these structures could arise, formally, via the ring opening of activated aziridines with *ortho*-halo phenyl metal reagents (Scheme 2). Aziridines are attractive starting materials, since procedures for the preparation of these compounds in chiral, non-racemic form are well established and efficient.[5]

Aryl lithium, aryl magnesium halide, and aryl zinc halide reagents have all been employed in the ring-opening reactions of aziridines.[6] These reactions typically require the use of copper additives, and both highly electrophilic (*N*-tosyl)[7] and moderately electrophilic (*N*-Cbz, *N*-Boc)[8] aziridines have been employed. Although reactions of aziridines with *ortho*-halo aryl lithium reagents have not been described in the literature,[9] the synthesis and reactivity of these reagents are known. While the parent *o*-bromophenyllithium and *o*-chlorophenyllithium species quickly decompose to form benzyne at temperatures above −100 °C and −78 °C,[10] respectively, compounds with additional stabilizing groups in the 6-position are stable at higher temperatures.[11] For example, 2,6-dibromophenyllithium is stable for several hours at −50 °C.[12] Alternatively, *ortho*-bromophenyl magnesium halides can be generated at −15 °C and undergo efficient copper cyanide-promoted 1,4-addition to enones at temperatures as high as 0 °C.[13] Finally, *ortho*-halo aryl zinc and copper reagents are stable at temperatures up to 40 °C.[14] The success of our approach would rely on the identification of *ortho*-halo aryl metal reagents that are sufficiently reactive to participate in ring-opening reactions of aziridines without undergoing competitive decomposition to benzyne. We report herein that aziridines can be opened efficiently with stabilized *ortho*-halo phenyllithium intermediates to afford phenethylamines suitable for cyclization to chiral 2-substituted indolines.



Scheme 1. General synthetic routes to indolines.



Scheme 2. Proposed synthesis of indolines via ring opening of aziridines.

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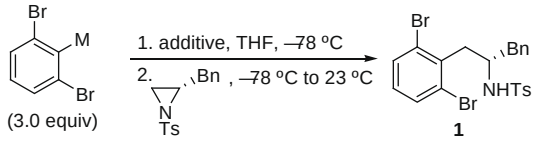
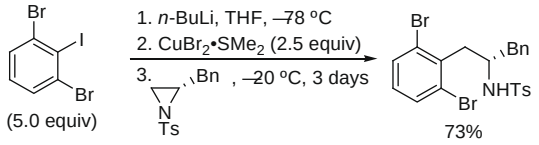
Table 1
Preliminary ring-opening reactions



Entry	[M]	Additive	Conversion[a] (%)
1	Li	none	10
2	Li	$BF_3{\cdot}OEt_2$	10
3	Li	$CuBr{\cdot}SMe_2$ (1.5 equiv)	70
4	ZnCl	$CuBr{\cdot}SMe_2$ (1.5 equiv)	0
5	MgCl	$CuBr{\cdot}SMe_2$ (0.2 equiv)	30

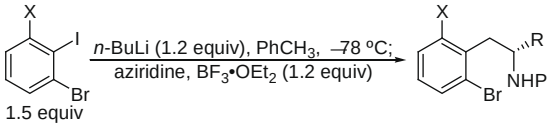
[a] As measured by ^{1}H NMR of the crude reaction mixtures.

We began our investigation by exploring the ring opening of (*S*)-2-benzyl-1-tosylaziridine with a variety of 2,6-dibromophenyl metal reagents (Table 1). Although the aryl lithium reagent could be generated directly from 1,3-dibromobenzene by deprotonation with LDA in THF at −78 °C, we found that formation of the aryl lithium via lithium-halogen exchange of 1,3-dibromo-2-iodobenzene with *n*-BuLi in THF ultimately provided cleaner reactions. Addition of the aziridine to a solution of 2,6-dibromophenyllithium (3.0 equiv) in THF at −78 °C followed by warming to room temperature over 24 h resulted in 10% conversion of the aziridine to the ring-opened product **1**, as judged by ^{1}H NMR analysis of the crude reaction mixture (Table 1, entry 1). Conversion did not increase in the presence of Lewis acids (e.g., boron trifluoride, entry 2), therefore we examined alternative organometallic agents. Formation of the corresponding organocuprate was best accomplished by exposure of the aryl lithium solution to copper bromide-dimethyl sulfide complex. Treatment of the resulting organocuprate solution with (*S*)-2-benzyl-1-tosylaziridine resulted in complete consumption of the aziridine and the appearance of product **1** (entry 3). However, the ^{1}H NMR spectrum of the crude mixture indicated that a number of undesired byproducts were formed. Use of the phenylzinc chloride or the phenylmagnesium chloride species



Scheme 3. Optimized ring opening with lithium organocuprate.

Table 2
Ring opening of aziridines with aryl lithium reagents



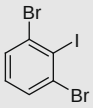
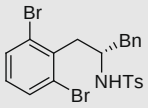
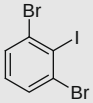
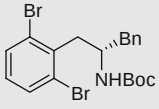
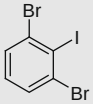
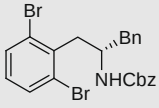
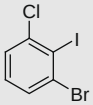
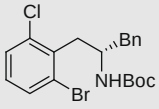
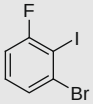
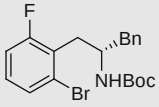
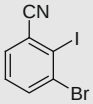
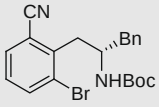
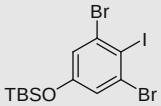
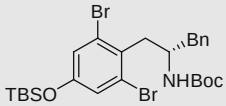
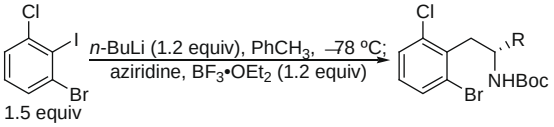
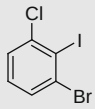
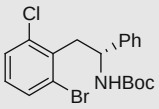
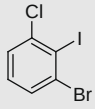
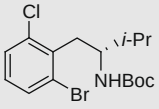
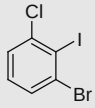
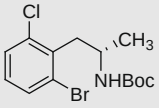
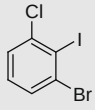
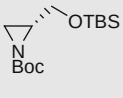
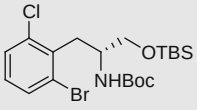
Entry	Ar-I	Aziridine	Product	Yield (%)
1				65
2				87
3				67
4				89
5				30
6				60
7				85

Table 3
Ring opening of *N*-Boc azirdines



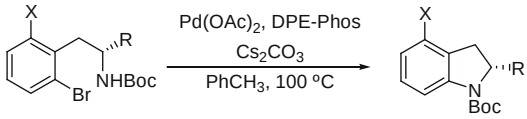
Entry	Ar-I	Aziridine	Product	Yield (%)
1				85
2				81
3				85
4				79

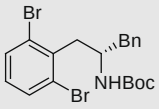
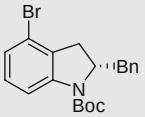
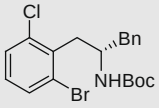
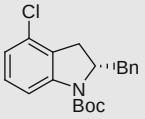
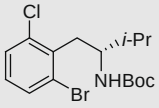
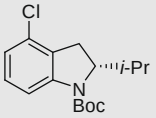
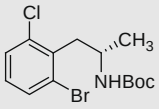
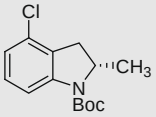
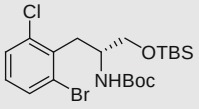
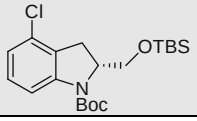
resulted in lower conversions to ring-opened product **1** (entries 4 and 5).

Since the lithium organocuprate provided the best conversion in our screen, we initially elected to optimize this reaction. After extensive experimentation (data not shown), we found that the best results were obtained when the aziridine was added to a solution of the lithium organocuprate (2.5 equiv) at −20 °C. After 3 days of reaction time, the ring-opened product was obtained in 73% yield following work-up and silica gel chromatography (Scheme 3). Although the desired product could be obtained in good yield, we felt that extended reaction times at low temperature and the need for a large excess of the starting aryl iodide would limit the utility of this procedure. Therefore, we elected to further examine the ring opening of aziridines with phenyllithium reagents in the presence of Lewis acid additives.

Although our initial attempts to utilize 2,6-dibromophenyllithium directly in the ring-opening reaction led to low conversions (Table 1, entries 1 and 2), we found that simply changing the reaction solvent to toluene resulted in much higher conversions.[15] In our optimized procedure, the aryl iodide[16] component (1.5 equiv) is treated with *n*-BuLi (1.2 equiv) in toluene at −78 °C to afford a solution of the phenyllithium reagent. Boron trifluoride diethyl etherate and the aziridine are added in sequence, and the resulting mixture is stirred for 2–4 h. As shown in Table 2, entry 1, the reaction employing 2,6-dibromophenyllithium and (*S*)-2-benzyl-1-tosylaziridine afforded phenethylamine **1** in 65% yield along with 10–15% recovered aziridine. We reasoned that competitive deprotonation of the aziridine by the phenyllithium reagent might be responsible for the incomplete conversion of aziridine to ring-opened product, so we next explored the use of less activated carbamate-protected aziridines. We were pleased to find that treatment of 2,6-dibromophenyllithium with (*S*)-*tert*-butyl 2-benzylaziridine-1-carboxylate under our optimized conditions resulted in an 87% yield of the corresponding phenethylamine (entry 2).[17] Surprisingly, the use of the Cbz-protected aziridine also produced the ring-opened product, although in a reduced 67% yield (entry 3). We further explored the substrate scope of the ring-opening reaction with (*S*)-*tert*-butyl 2-benzylaziridine-1-carboxylate. The reaction with (2-bromo-6-chlorophenyl)lithium gave the phenethylamine product in 89% yield (entry 4); however, the less stable (2-bromo-6-fluorophenyl)lithium produced the ring-opened product in only 30% yield (entry 5).[10c] The use of (2-bromo-6-cyanophenyl)lithium also afforded the desired phenethylamine in a moderate 60% yield (entry 6). Finally, additional oxygenation of the aryl ring was well tolerated (entry 7).

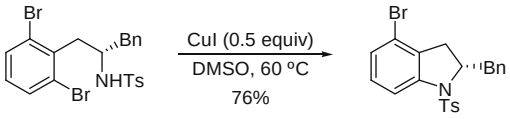
Table 4
Cyclization reactions to form indolines



Entry	Substrate	Product	Yield (%)
1			51
2			97
3			51
4			76
5			97

We next explored ring-opening reactions of (2-bromo-6-chlorophenyl)lithium with a variety of *N*-Boc-protected 1-substituted aziridines. As shown in Table 3, phenyl substitution was well tolerated, as the ring-opening reaction of (*S*)-*tert*-butyl 2-phenylaziridine-1-carboxylate cleanly provided the desired product in 85% yield (entry 1). In addition, aziridines with both large and small (entries 2 and 3) alkyl substituents functioned efficiently in the ring-opening reaction, as did an aziridine with a silyloxymethyl substituent (entry 4).

Having established procedures for the synthesis of *ortho*-bromo phenethylamines via the ring opening of aziridines, we sought to confirm that these products could be transformed to 2-substituted indolines. As shown in Table 4, exposure of *N*-Boc *ortho*-bromo phenethylamines to catalytic palladium acetate and DPE-Phos in the presence of cesium carbonate in toluene afforded the desired indoline products in moderate to very good yields in this unoptimized procedure.[2d] Additionally, cyclization of an *N*-tosyl *ortho*-bromo phenethylamine could be accomplished by exposure to copper iodide (0.5 equiv) in DMSO at 60 °C to afford the indoline product in good yield (Scheme 4).



Scheme 4. Cu-catalyzed cyclization of an *N*-tosyl-protected phenethylamine.

In conclusion, we have demonstrated that mono-substituted aziridines undergo efficient ring opening with stabilized *ortho*-bromo phenyl metal reagents. Although *N*-tosyl aziridines could be opened with lithium organocuprates in good yields, the use of phenyllithium reagents in conjunction with boron trifluoride as a Lewis acid in toluene as solvent provided a more general method. With this method *N*-tosyl, *N*-Boc, and *N*-Cbz-activated aziridines undergo ring opening to give the desired *ortho*-bromo phenethylamine products. Further, we have demonstrated that the *ortho*-bromo phenethylamine products undergo efficient transition-metal-catalyzed cyclization to form chiral, non-racemic 2-substituted indolines. Further studies with stabilized *ortho*-bromo phenyllithium reagents and additional applications of *ortho*-bromo phenethylamines will be reported in due course.

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References and notes

1. (a) Cignarella, G.; Sanna, P. *J. Med. Chem.* **1981**, *24*, 1003–1006; (b) Hlasta, D. J.; Luttinger, D.; Perrone, M. H.; Silbernagel, M. J.; Ward, S. J.; Haubrich, D. R. *J. Med. Chem.* **1987**, *30*, 1555–1562; (c) Bermudez, J.; Dabbs, S.; Joiner, K. A.; King, F. D. *J. Med. Chem.* **1990**, *33*, 1929–1932; (d)*The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 50.
2. (a) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451–8558; (b) Deboves, H. J. C.; Hunter, C.; Jackson, R. F. W. *J. Chem. Soc., Perkin. Trans. 1* **2002**, 733–736; (c) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron Lett.* **2003**, *44*, 2569–2572; (d) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35–37.
3. (a) Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721–2724. and references cited therein; (b) Aoki, K.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 3068–3073; (c) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, 5255–5258; (d) Li, K.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452–6455.
4. (a) Gross, K. M. B.; Jun, Y. M.; Beak, P. *J. Org. Chem.* **1997**, *62*, 7679–7689; (b) Viswanathan, R.; Mutnick, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *123*, 7266–7271; (c) Srinivasan, J. M.; Burks, H. E.; Smith, C. R.; Viswanathan, R.; Johnston, J. N. *Synthesis* **2005**, *2*, 330–333; (d) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777–4779.
5. (a) Aggarwal, V. K.; Badine, M. D.; Moorthie, V. A. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2006. pp 1–35; (b) Wessig, P.; Schwarz, J. *Synlett* **1997**, 893–894.
6. For reviews, see: (a) McCoull, W.; Davis, F. A. *Synthesis* **2000**, *10*, 1347–1365; (b) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743; (c) Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979–4988.
7. (a) Hudlicky, T.; Tian, X.; Königsberger, K.; Rouden, J. *J. Org. Chem.* **1994**, *59*, 4037–4039; (b) Toshimitsu, A.; Abe, H.; Hirosawa, C.; Tamao, K. *J. Chem. Soc., Perkin. Trans. 1* **1994**, 3465–3471; (c) Beresford, K. J. M.; Church, N. J.; Young, D. W. *Org. Biomol. Chem.* **2006**, *4*, 2888–2897; (d) Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643–3644.
8. (a) Baldwin, J. E.; Farthing, C. N.; Russell, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett.* **1996**, *37*, 3761–3764; (b) Chakraborty, T. K.; Gangakhedkar, K. K. *Synth. Commun.* **1996**, *26*, 2045–2056; (c) Travins, J. M.; Etzkorn, F. A. *Tetrahedron Lett.* **1998**, *39*, 9389–9392; (d) Achmatowicz, M.; Chan, J.; Wheeler, P.; Liu, L.; Faul, M. M. *Tetrahedron Lett.* **2007**, *48*, 4825–4829.
9. Three examples of aziridine ring opening with *ortho*-fluoro substituted aryl magnesium halide reagents are described in: Zhu, G.-D.; Ghandi, V. B.; Gong, J.; Thomas, S.; Woods, K. W.; Song, X.; Li, T.; Diebold, R. B.; Luo, Y.; Liu, X.; Guan, R.; Klinghofer, V.; Johnson, E. F.; Bouska, J.; Olson, A.; Marsh, K. C.; Stoll, V. C.; Mamo, M.; Polakowski, J.; Campbell, T. J.; Martin, R. L.; Gintant, G. A.; Penning, T. D.; Li, Q.; Rosenberg, S. H.; Giranda, V. L. *J. Med. Chem.* **2007**, *50*, 2990–3003. However, these examples all involved bis-fluorinated arenes and experimental details are not provided.
10. (a) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1956**, *78*, 2217–2222; (b) Prabhu, U. D. G.; Eapen, K. C.; Tamborski, C. *J. Org. Chem.* **1984**, *49*, 2792–2795; For a detailed examination of the decomposition of 2-chloro-6-fluorophenyllithium into benzynes, see: (c) Riggs, J. C.; Ramirez, A.; Cremeens, M. E.; Bashore, C. G.; Candler, J.; Wirtz, M. C.; Coe, J. W.; Collum, D. B. *J. Am. Chem. Soc.* **2008**, *130*, 3406–3412.
11. (a) Iwao, M. *J. Org. Chem.* **1990**, *55*, 3622–3627; (b) Castagnetti, E.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 691–695; (c) Leroux, F.; Schlosser, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4272–4274; (d) Gohier, F.; Mortier, J. *J. Org. Chem.* **2003**, *68*, 2030–2033; (e) Schlosser, M.; Cottet, F.; Heiss, C.; Lefebvre, O.; Marull, M.; Masson, E.; Scopelliti, R. *Eur. J. Org. Chem.* **2006**, 729–734.
12. Luliński, S.; Seratowski, J. *J. Org. Chem.* **2003**, *68*, 5384–5387.
13. (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701–1703; (b) Krasovsky, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333–3336.
14. (a) Ebert, G. W.; Pfennig, D. R.; Suchan, S. D.; Donovan, T. A., Jr.; Aouad, E.; Tehrani, S. S.; Gunnersen, J. N.; Dong, L. *J. Org. Chem.* **1995**, *60*, 2361–2364; (b) Takahashi, H.; Hossain, K. M.; Nishihara, Y.; Shibata, T.; Takagi, K. *J. Org. Chem.* **2006**, *71*, 671–675.
15. For an example of a reaction between a 2,6-dibromophenyllithium species and an epoxide using toluene as solvent, see: Okano, K.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7136–7137.
16. Aryl iodides were generated via deprotonation of the corresponding 1,3-dihalobenzenes with LDA and quenching of the aryllithium intermediate with iodine. For the syntheses of 1-bromo-3-chloro-2-iodobenzene and 1-bromo-3-fluoro-2-iodobenzene, the aryllithium intermediate was treated with zinc chloride prior to the iodine quench, according to the procedure of: Menzel, K.; Fisher, E. L.; DiMichele, L.; Frantz, D. E.; Nelson, T. D.; Kress, M. H. *J. Org. Chem.* **2006**, *71*, 2188–2191.
17. *Representative procedure*: A 10-mL round-bottomed flask was charged with *n*-BuLi (0.23 mL of a 2.20 M solution in hexane, 0.51 mmol, 1.2 equiv) and toluene (0.6 mL). The resulting solution was cooled to −78 °C, then a solution of 1,3-dibromo-2-iodobenzene (232 mg, 0.64 mmol, 1.5 equiv) in toluene (0.9 mL) was added dropwise via syringe. The mixture was stirred for 30 min to give a white slurry, and boron trifluoride-diethyl etherate (65 μL, 0.64 mmol, 1.5 equiv) and a solution of (*R*)-*tert*-butyl 2-benzylaziridine-1-carboxylate (100 mg, 0.43 mmol) in toluene (0.7 mL) were added in sequence. The resulting mixture was stirred at −78 °C for 2 h, then was quenched with methanol (1 mL). After warming to room temperature, the reaction mixture was diluted with brine (4 mL), and the aqueous mixture was extracted with dichloromethane (3 × 6 mL). The organic extracts were combined, and the combined solution was dried over sodium sulfate, filtered, and evaporated. The crude product was purified by chromatography on silica gel (eluting with 5–20% ethyl acetate in hexane) to give (*S*)-*tert*-butyl 1-(2,6-dibromophenyl)-3-phenylpropan-2-ylcarbamate (180 mg, 87% yield) as a white solid. At room temperature, this compound existed as a 3:1 mixture of rotamers in DMSO-d_6 on the NMR timescale, and the two sets of peaks coalesced at ca. 60 °C. Data for the major rotamer: ^{1}H NMR (600 MHz, DMSO-d_6, 23 °C) δ ppm 7.58 (d, J = 7.9 Hz, 2H), 7.15–7.28 (m, 6H), 7.04 (t, J = 8.1 Hz, 1H), 6.67 (d, J = 9.5 Hz, 1H), 4.06–4.16 (m, 1H), 3.15 (dd, J = 13.4, 9.5 Hz, 1H), 3.03 (dd, J = 13.4, 4.6 Hz, 1H), 2.91 (dd, J = 13.7, 9.5 Hz, 1H), 2.72 (dd, J = 13.6, 5.3 Hz, 1H), 1.17 (s, 9H).