ORGANIC LETTERS

2010
Vol. 12, No. 16
3716−3719

Copper-Catalyzed Intramolecular *N*-Arylation of Quinazolinones: Facile Convergent Approach to (−)-Circumdatins H and J

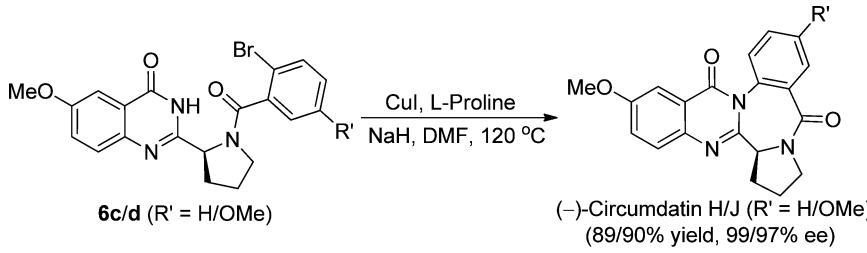
Umesh A. Kshirsagar and Narshinha P. Argade*

Division of Organic Chemistry, National Chemical Laboratory (CSIR), Pune 411 008, India

np.argade@ncl.res.in

Received July 12, 2010

ABSTRACT



A copper-catalyzed intramolecular *N*-arylation of a quinazolinone nucleus that furnished the central benzodiazepine core unit has been demonstrated to accomplish an efficient convergent total synthesis of (−)-circumdatins H and J.

Quinazolinones are an important class of compounds, and a large number of structurally interesting and biologically important natural and synthetic quinazolinones are known in the literature.[1] Presently, some quinazolinones are in clinical use,[1,2] and on the basis of their structural architecture and promising bioactivities they have been important target compounds.[3] Circumdatins are the marine natural products from fungi of the genus *Aspergillus*, and they possess antitumor, antifungal, insecticide, and antibiotic activities (Figure 1).[4] (−)-Circumdatins H and J have been recently isolated from *Aspergillus ochraceus* and *Aspergillus ostianus*, respectively, and more specifically, the (−)-circumdatin H is an inhibitor of the mammalian mitochondrial respiratory chain, with an IC_{50} value of 1.5 μM.[5] Circumdatins are basically the quinazolinobenzodiazepines, and the provision of new efficient synthetic routes to them is the pivotal task of current interest.[6,7] Very recently, syntheses of (−)-circumdatins H and J have been reported by using an intramolecular aza-Wittig reaction and reductive cyclization as the key steps.[7] Metal-catalyzed C(aryl)−N bond-forming

(1) (a) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 348. (b) Roy, A. D.; Subramanian, A.; Roy, R. *J. Org. Chem.* **2006**, *71*, 382, and references cited therein. (c) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787, and references cited therein.

(2) (a) Amin, A. H.; Mehta, D. R.; Samarth, S. S. *Prog. Drug. Res.* **1970**, *14*, 218. (b) Johne, S. *Prog. Drug. Res.* **1982**, *26*, 259. (c) Johne, S. *Prog. Chem. Org. Nat. Prod.* **1984**, *46*, 159. (d) Sinha, S.; Srivastava, M. *Prog. Drug. Res.* **1994**, *43*, 143.

(3) (a) Malgesini, B.; Forte, B.; Borghi, D.; Quartieri, F.; Gennari, C.; Papeo, G. *Chem.—Eur. J.* **2009**, *15*, 7922. (b) Xiao, Z.; Yang, M. G.; Li, P.; Carter, P. H. *Org. Lett.* **2009**, *11*, 1421. (c) Toumi, M.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 5027. (d) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (e) Snider, B. B.; Wu, X. *Org. Lett.* **2007**, *9*, 4913. (f) Zhichkin, P.; Kesicki, E.; Treiberg, J.; Bourdon, L.; Ronsheim, M.; Ooi, H. C.; White, S.; Judkins, A.; Fairfax, D. *Org. Lett.* **2007**, *9*, 1415. (g) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417.

(4) (a) Rahbæk, L.; Breinholt, J.; Frisvad, J. C.; Christophersen, C. *J. Org. Chem.* **1999**, *64*, 1689. (b) Rahbæk, L.; Breinholt, J. *J. Nat. Prod.* **1999**, *62*, 904. (c) Dai, J.-R.; Carte, B. K.; Sidebottom, P. J.; Yew, A. L. S.; Ng, S.-B.; Huang, Y.; Butler, M. S. *J. Nat. Prod.* **2001**, *64*, 125. (d) Zhang, D.; Yang, X.; Kang, J. S.; Choi, H. D.; Son, B. W. *J. Antibiot.* **2008**, *61*, 40.

(5) (a) Lopez-Gresa, M. P.; Gonzalez, M. C.; Primo, J.; Moya, P.; Romero, V.; Estornell, E. *J. Antibiot.* **2005**, *58*, 416. (b) Ookura, R.; Kito, K.; Ooi, T.; Namikishi, M.; Kusumi, T. *J. Org. Chem.* **2008**, *73*, 4245.

10.1021/ol101597p
Published on Web 07/29/2010

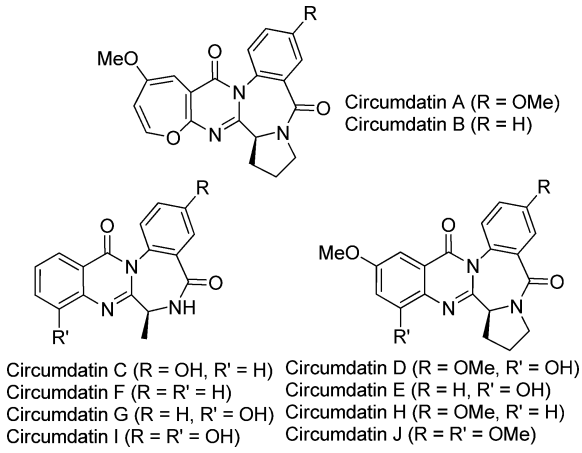


Figure 1. Naturally occurring bioactive circumdatins A−J.[4,5]

reactions under mild catalytic conditions utilizing amines, amides, and nitrogen heterocycles are imperative from a synthetic point of view to design the exotic natural products and synthetic compounds.[8−11] However, metal-catalyzed intramolecular *N*-arylation of quinazolinones has not been studied, to the best of our knowledge.[1,2] In continuation of our studies on quinazolinone chemistry,[12] we envisaged the metal-catalyzed intramolecular *N*-arylation of quinazolinones implementing the advanced Goldberg−Buchwald protocol[9,10] that would provide an efficient access to a large number of desired naturally occurring quinazolinones and their analogues and congeners. In this context, we herein report our results on copper-catalyzed intramolecular *N*-arylation of the quinazolinone nucleus and its application in the synthesis of (−)-circumdatins H and J (Schemes 1 and 2).

Careful scrutiny of circumdatin skeletons revealed that nature most likely utilizes two appropriate anthranilic acid units and L-proline/L-alanine to create them. We planned our biogenetic-type synthesis of circumdatin framework starting from anthranilamide and L-proline via the corresponding potential quinazolinone intermediate **6a** (Scheme 1). We could foresee that our major challenges would be in the metal-catalyzed intramolecular *N*-arylation of quinazolinones to form the intricate seven-membered diazepine cores and the complete conservation of enantiomeric purity throughout the synthesis. The EDCI-induced dehydrative coupling of the Boc-protected L-proline (**2**) with anthranilamide (**1**) at room temperature furnished the diamide **3** in 87% yield. The subsequent base-catalyzed intramolecular dehydrative cyclization of compound **3** provided the required quinazolinone **4** in 92% yield. The TFA deprotection of the Boc group in compound **4**, followed by the dehydrative couplings of thus-formed intermediate free amine **5** with 2-bromobenzoic acid and 2-bromo-5-methoxybenzoic acid, furnished the desired precursors **6a/b** in 85/83% yield but, unfortunately, with complete racemization in both the cases. Herein, the acid-catalyzed racemization of our substrate **5** took place during the TFA-induced Boc-deprotection step, plausibly because of the presence of an adjacent imine funtionality from the quinazolinone moiety. We first studied the palladium-catalyzed intramolecular *N*-arylation of quinazolinone **6a** under a variety of reaction conditions using different promising ligands (xantphos, BINAP, johnphos), bases (Cs_2CO_3/NaOBu^t), and solvents (toluene/1,4-dioxane) at elevated temperature, but unfortunately, all our attempts met

(6) (a) Tseng, M.-C.; Yang, H.-Y.; Chu, Y.-H. *Org. Biomol. Chem.* **2010**, *8*, 419. (b) Tseng, M.-C.; Lai, C.-Y.; Chu, Y.-W.; Chu, Y.-H. *Chem. Commun.* **2009**, 445. (c) Liu, J.-F.; Kaselj, M.; Isome, Y.; Chapnick, J.; Zhang, B.; Bi, G.; Yohannes, D.; Yu, L.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 10488. (d) Snider, B. B.; Busuyek, M. V. *Tetrahedron* **2001**, *57*, 3301. (e) Witt, A.; Bergman, J. *J. Org. Chem.* **2001**, *66*, 2784.

(7) (a) Zhichkin, P. E.; Jin, X.; Zhang, H.; Peterson, L. H.; Ramirez, C.; Snyder, T. M.; Burton, H. S. *Org. Biomol. Chem.* **2010**, *8*, 1287. (b) Bose, D. S.; Chary, M. V. *Synthesis* **2010**, 643.

(8) (a) Maiti, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 17423. (b) Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049. (c) Bhagwanth, S.; Waterson, A. G.; Adjabeng, G. M.; Hornberger, K. R. *J. Org. Chem.* **2009**, *74*, 4634. (d) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505. (e) Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584. (f) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523. (g) Venkatesh, C.; Sundaram, G. S. M.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2006**, *71*, 1280. (h) Dallas, A. S.; Gothelf, K. V. *J. Org. Chem.* **2005**, *70*, 3321. (i) Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14475. (j) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2004**, *6*, 2433. (k) Wang, T.; Magnin, D. R.; Hamann, L. G. *Org. Lett.* **2003**, *5*, 897. (l) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (m) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101. (n) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35. (o) Hartwig, J. F. *Angew Chem., Int. Ed.* **1998**, *37*, 2046, and references cited therein.

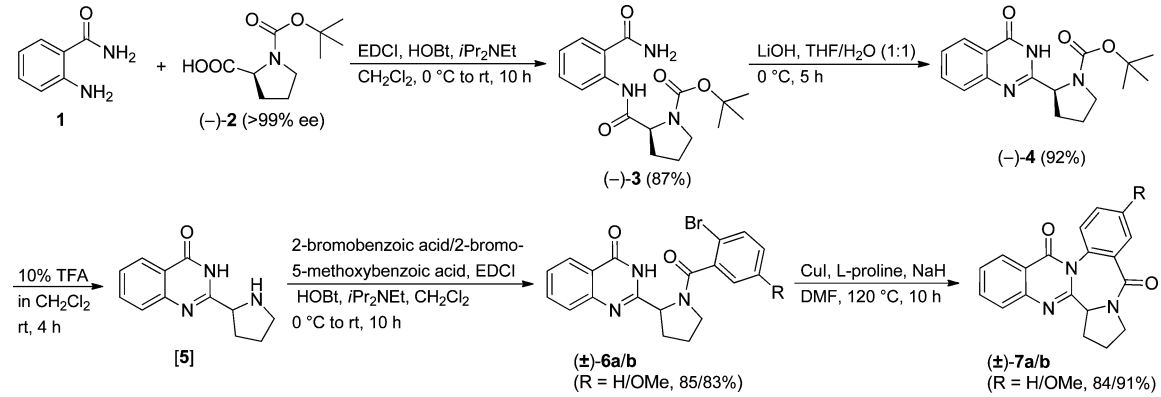
(9) (a) Jouvin, K.; Couty, F.; Evano, G. *Org. Lett.* **2010**, *12*, 3272. (b) Gong, X.; Yang, H.; Liu, H.; Jiang, Y.; Zhao, Y.; Fu, H. *Org. Lett.* **2010**, *12*, 3128. (c) Wang, Z.-J.; Yang, J.-G.; Yang, F.; Bao, W. *Org. Lett.* **2010**, *12*, 3034. (d) Wang, Y.; Liao, Q.; Xi, C. *Org. Lett.* **2010**, *12*, 2951. (e) Lim, H. J.; Gallucci, J. C.; RajanBabu, T. V. *Org. Lett.* **2010**, *12*, 2162. (f) Cortes-Salva, M.; Nguyen, B.-L.; Cuevas, J.; Pennypacker, K. R.; Antilla, J. C. *Org. Lett.* **2010**, *12*, 1316. (g) Tye, J. W.; Weng, Z.; Johns, A. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 9971. (h) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78. (i) Yang, C.-T.; Fu, Y.; Huang, Y.-B.; Yi, J.; Guo, Q.-X.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 7398. (j) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (k) Liang, L.; Li, Z.; Zhou, X. *Org. Lett.* **2009**, *11*, 3294. (l) Diao, X.; Wang, Y.; Giang, Y.; Ma, D. *J. Org. Chem.* **2009**, *74*, 7974. (m) Kumar, S.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2009**, *74*, 7046. (n) Deng, X.; McAllister, H.; Mani, N. S. *J. Org. Chem.* **2009**, *74*, 5742. (o) Lv, X.; Bao, W. *J. Org. Chem.* **2009**, *74*, 5618. (p) Jiang, L.; Lu, X.; Zhang, H.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2009**, *74*, 4542. (q) Zhu, L.; Li, G.; Luo, L.; Guo, P.; Lan, J.; You, J. *J. Org. Chem.* **2009**, *74*, 2200. (r) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096. (s) Zhao, Q.; Li, C. *Org. Lett.* **2008**, *10*, 4037. (t) Li, Z.; Sun, H.; Jiang, H.; Liu, H. *Org. Lett.* **2008**, *10*, 3263. (u) Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721. (v) Jones, K. L.; Porzelle, A.; Hall, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Org. Lett.* **2008**, *10*, 797. (w) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452. (x) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 643. (y) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968. (z) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190.

(10) (a) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (b) Zhu, L.; Cheng, L.; Zhang, Y.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 2737. (c) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653. (d) Ghosh, A.; Sieser, J. E.; Caron, S.; Couturier, M.; Dupont-Gaudet, K.; Girardin, M. *J. Org. Chem.* **2006**, *71*, 1258. (e) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120. (f) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400, and references cited therein. (g) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133. (h) Antilla, J. C.; Kalpars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (i) Kalpars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421, and references cited therein.

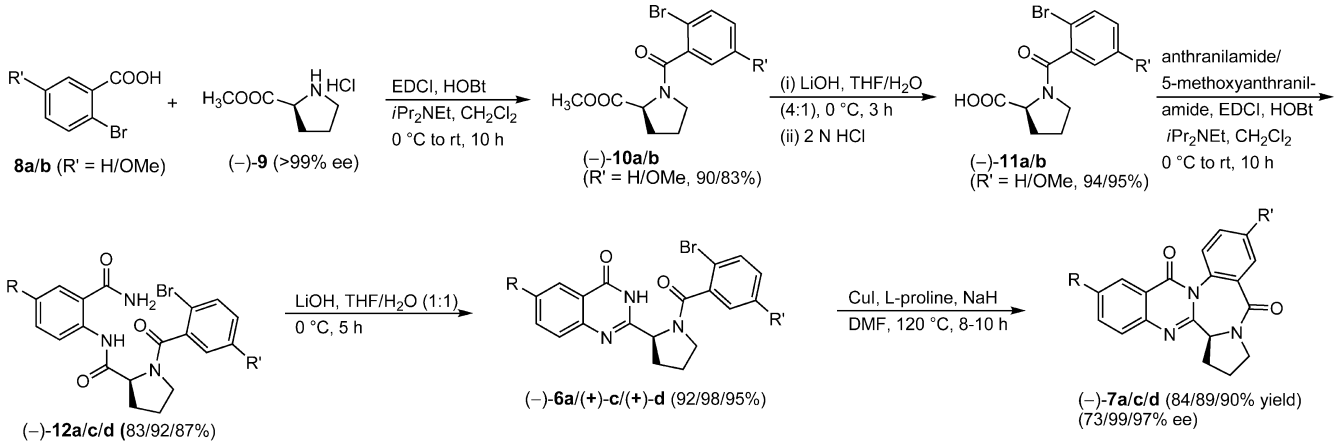
(11) Ikegai, K.; Nagata, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 761.

(12) (a) Kshirsagar, U. A.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2010**, *75*, 2702. (b) Kshirsagar, U. A.; Argade, N. P. *Tetrahedron* **2009**, *65*, 5244. (c) Kshirsagar, U. A.; Mhaske, S. B.; Argade, N. *P Tetrahedron Lett.* **2007**, *48*, 3243. (d) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2004**, *69*, 4563. (e) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2004**, *60*, 3417. (f) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2001**, *66*, 9038.

Scheme 1. Synthesis of Circumdatin Frameworks **7a/b** via the Intramolecular *N*-Arylation of Quinazolinones **6a/b**



Scheme 2. Copper-Catalyzed Intramolecular *N*-Arylation of Quinazolinones: Synthesis of Circumdatins H (**7c**) and J (**7d**)



[for **6**/**7**/**12**, **a**: R = R' = H; **c**: R = OMe, R' = H; **d**: R = R' = OMe]

with failure and we always recovered starting material, the compound **6a** (Table 1, entries 1−4). The palladium-catalyzed *N*-arylations are known to have some limitations,[9h] and hence, we decided to screen cheap and versatile copper catalysts for the intramolecular cyclization of compound **6a** to form **7a** using different ligands.[9,10] We noticed that the copper iodide catalyzed intramolecular *N*-arylation of compound **6a** using 8-hydroxyquinoline/2-oxazolidinone ligands was feasible, and we could obtain the desired product **7a**, but in low yields (Table 1, entries 5 and 6). All our attempts to further improve the yield by changing the molar ratios and reaction conditions were unsuccesful. Finally, we were delighted to learn that the copper-catalyzed regioselective intramolecular cross-coupling between the 3-position nitrogen atom in the polar quinazolinone **6a** and an adjacent aryl bromide using L-proline as the ligand and sodium hydride as the base in the solvent DMF at 120 °C exclusively furnished the desired thermodynamically more stable linear product **7a** in 84% yield (Table 1, entry 7). The circumdatin J has the methoxy group in the nonquinazolinone aromatic ring, and hence, at this stage we also studied the intramolecular *N*-arylation of compound **6b**. Similarly, the reaction

Table 1. Optimization of Reaction Conditions for the Metal-Catalyzed Intramolecular *N*-Arylation of Quinazolinones **6a/b**

entry	reaction conditions[a]	**7a/b** (% yield)
1	$Pd(OAc)_2$, xantphos, Cs_2CO_3, dioxane, 100 °C, 24 h	**7a** (NR)[b]
2	$Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C, 24 h	**7a** (NR)
3	$Pd_2(dba)_3$, xantphos, Cs_2CO_3, dioxane, 100 °C, 24 h	**7a** (NR)
4	$Pd_2(dba)_3$, johnphos, *t*-BuONa, toluene, 100 °C, 24 h	**7a** (NR)
5	CuI, 8-hydroxyquinoline, K_2CO_3, DMSO, 120 °C, 24 h	**7a** (11)
6	CuI, 2-oxazolidinone, MeONa, DMSO, 120 °C, 24 h	**7a** (30)
7	CuI, L-proline, NaH, DMF, 120 °C, 10 h	**7a** (84)
8	CuI, L-proline, NaH, DMF, 120 °C, 10 h	**7b** (91)

[a] 20 mol % of catalyst; 30 mol % of ligand, and 2 equiv of base were used in all the entries. [b] NR: no reaction.

of compound **6b** under the above-mentioned reaction conditions provided the desired product **7b** in 91% yield (Table 1, entry 8). Herein, mechanistically the bond formation between ligand-coordinated copper iodide and quinazolinone nitrogen atom followed by the copper-catalyzed intramolecular cross-coupling with an aryl bromide which generates the new carbon−nitrogen bond to deliver the middle diazepine ring is significant from a synthetic point of view. Thus, the racemic circumdatin frame works **7a/b** were obtained in five steps with 57/61% overall yields, and the obtained analytical and spectral data for the compound **7a** were in complete agreement with the reported data.[6b]

To circumvent the associated problem of racemization in our above-described Scheme 1 and also to accomplish the synthesis of enantiomerically pure natural products, the (−)-circumdatins **7c** and **7d**, we reasoned and decided to suitably alter our synthetic sequence. In our second approach, we planned to avoid the use of Boc-protected proline and its subsequent TFA-catalyzed deprotection for the conservation of enantiomeric excess. Hence, we first performed the EDCI-induced dehydrative couplings of the 2-bromobenzoic acid (**8a**) and 2-bromo-5-methoxybenzoic acid (**8b**) with the methyl ester of L-proline (**9**) and respectively obtained the corresponding products (−)-**10a**[13]**/b** in 90/83% yields (Scheme 2). The subsequent base-catalyzed ester hydrolysis of (−)-**10a/b** followed by the careful acidification with dilute hydrochloric acid provided the corresponding *N*-benzoylprolines (−)-**11a/b** in high yields. Once again, the EDCI-induced dehydrative couplings of compound (−)-**11a** with both the anthranilamide and 5-methoxyanthranilamide and (−)-**11b** with 5-methoxyanthranilamide, respectively, provided the corresponding triamides (−)-**12a/c/d** in 83−92% yields. The triamides (−)-**12a/c/d** on base-catalyzed selective intramolecular dehydrative cyclization furnished the essential quinazolinones (−)-**6a/**(+)-**c/**(+)-**d** in 92−98% yields. Thus, by altering the reaction sequence we were successful in avoiding the problem of racemization in the preparation of our potential precursors **6a/c/d**, required for the synthesis of compounds (−)-**7a/c/d**. Finally, we decided to expose the requisite quinazolinones **6a/c/d** to our previously established efficient copper-catalyzed intramolecular *N*-arylation conditions as described in entries 7 and 8 of Table 1. The copper-catalyzed intramolecular *N*-arylation of compounds **6a/c/d** using L-proline as the ligand and sodium hydride as the base in solvent DMF at 120 °C exclusively furnished the desired final products, the synthetic and natural quinazolinones (−)-**7a/c/d** in 84−90% yields. Thus, the desired products (−)-**7a/c/d** were obtained in five steps with 54/68/59% overall yields, and the obtained analytical and spectral data for the natural products (−)-circumdatins H and J (**7c**,**d**) were in complete agreement with the reported data.[5,7] Starting from the (±)-methyl ester of proline, we similarly synthesized the racemic products **7c/d** required for the comparison and then checked the enantiomeric purity of our final products (−)-**7a/c/d** by chiral HPLC. The chiral HPLC results revealed that we obtained the circumdatin framework product (−)-**7a** with 73% ee and the (−)-circumdatins H/J (**7c/d**) with 99/97% ee. These results on the conserved enantiomeric purity of (−)-**7a/c/d** clearly indicate that the compounds (−)-**6a** and/or (−)-**7a** experience ∼13% racemization under basic conditions, while the (−)-circumdatins H/J (**7c/d**) with the suitably placed methoxy group in ring A were not prone for such type of racemization under the set of our reaction conditions as depicted in Scheme 2. We believe the π-conjugation of methoxy group with an imine moiety from the quinazolinone ring is responsible for the preclusion of racemization at an adjacent allylic asymmetric center in the compounds (−)-**7c/d**. The enantiomerically pure circumdatins H and J are also the likely biosynthetic precursors of circumdatins B and A, respectively.[5b]

In summary, we have reported the concise and efficient total synthesis of (−)-circumdatins H and J by demonstrating the first copper-catalyzed intramolecular *N*-arylation of quinazolinone with the noteworthy generation of a central benzodiazepine unit. We believe our approach has broad scope and will be useful in the synthesis of a diverse range of desired natural and unnatural complex quinazolinones for SAR studies.

Acknowledgment. U.A.K. thanks CSIR, New Delhi, for the award of a research fellowship. N.P.A. thanks the Department of Science and Technology, New Delhi, for financial support. We thank Dr. S. S. Kunte from NCL, Pune, for the HPLC data.

Supporting Information Available: Experimental procedures for the preparation of compounds **3**, **4**, **10a**,**b**, **11a**,**b**, **12a**,**c**,**d**, **6a**−**d**, and **7a**−**d** along with their tabulated analytical and spectral data. ^{1}H NMR, ^{13}C NMR, and DEPT spectra of compounds **3**, **4**, **10a**,**b**, **11a**,**b**, **12a**,**c**,**d**, **6a**−**d**, and **7a**−**d**. HPLC data for the enantiomeric purity of the compounds **7a**,**c**,**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101597P

(13) Sato, T.; Kugo, Y.; Nakaumi, E.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1801.