Natural Product Synthesis

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Dearomatizing Conjugate Addition to Quinolinyl Amidines for the Synthesis of Dehaloperophoramidine through Tandem Arylation and Allylation**

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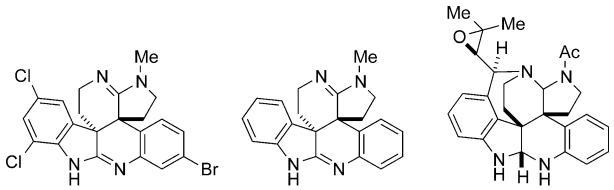
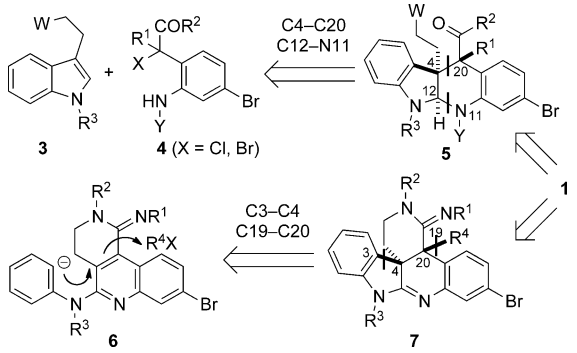
In 2002, Ireland and co-workers reported the isolation of perophoramidine (**1**) from the Philippine ascidian *Perophora namei*, and revealed that this alkaloid exhibited cytotoxicity toward HCT116 colon carcinoma cells. The compound consists of an unusual and unique hexacyclic bisamidine structure that contains two contiguous all-carbon quaternary centers as the core structure and halogen atoms on the aromatic rings.[1] Communesins[2] bearing a bisaminal motif instead of a bisamidine are architecturally related to perophoramidine and include a total of eight natural products.



The intriguing biological activities and unique chemical structures of these natural products have attracted the attention of synthetic chemists, and substantial effort has been applied toward their total synthesis and other synthetic studies.[3,4] The first total synthesis of (±)-**1** was accomplished by Funk an Fuchs[5a] in 2004, using a Diels–Alder reaction as a key step. In 2010, Qin and co-workers[5b] achieved the asymmetric total synthesis of (+)-**1** using chiral diene precursors, and they determined its absolute configuration. The total synthesis of **1** relies on the same [4+2] cycloaddition strategy via the synthones **3** and **4**, as represented by the biomimetic Diels–Alder reaction,[4a,c] for the construction of the polycyclic core structure **5**, including the contiguous quaternary stereogenic centers (Scheme 1). Thus far, five total syntheses of the communesins have been reported.[6]



Scheme 1. Synthetic strategies for the concurrent formation of contiguous quaternary stereogenic centers at C4 and C20.

Most of these synthetic routes are based on the same disconnection approach.

Dehaloperophoramidine (**2**) is a dehalogenated derivative of **1** and was first synthesized through a hydrogenolysis reaction of the natural product by its discoverers.[1] Later in 2006, Rainier and co-workers reported the synthesis of (±)-**2** from a tryptamine derivative through a similar retrosynthetic analysis involving stepwise C4–C20, C12–N11, and C3–C4 bond formations.[7] Toward a unique synthetic strategy distinct from the reported strategies,[3a,c–e,g,h] we envisioned an intramolecular conjugate addition of the in situ generated aryl anion **6** to a quinolinyl amidine moiety and the subsequent stereoselective alkylation of the resulting lithium azaenolate. This strategy for synthesizing **7** features the simultaneous assembly of the contiguous stereogenic centers C4 and C20 and the requisite bisamidine unit in a single operation that does not involve the oxidation of an aminal intermediate.

Our retrosynthetic analysis is described in Scheme 2. The A ring of **2** was constructed from the pentacyclic bisamidine **8**, which could be synthesized by an intramolecular dearomatizing cyclization reaction initiated by the lithium–iodine exchange of the iodinated aminoquinoline **9** and the subsequent α-allylation of the resultant amidine. The usual procedure was anticipated to yield quinolinyl amidine **9** from the corresponding amide **10**, which was derived from carbodiimide **11** through a thermal 6π-electrocyclic reaction between the unsaturated lactam and the carbodiimide moieties.[8] We expected that the desulfurization of thiourea **12**, prepared by a sequential coupling of bromolactam **13**,[9] boronic acid **14**,[10] and isothiocyanate **15**, would provide the desired carbodiimide **11**.

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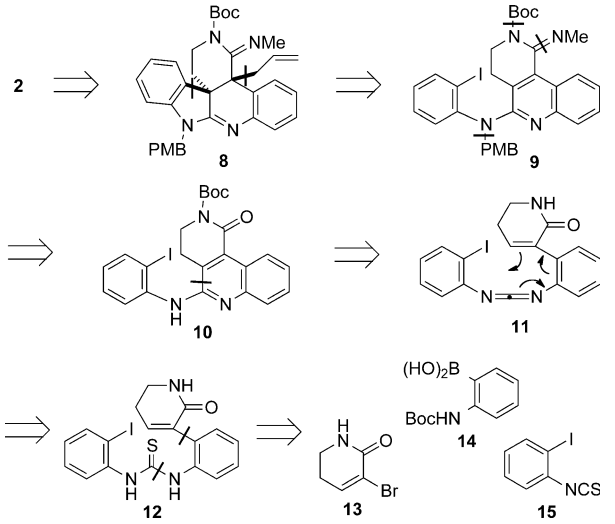
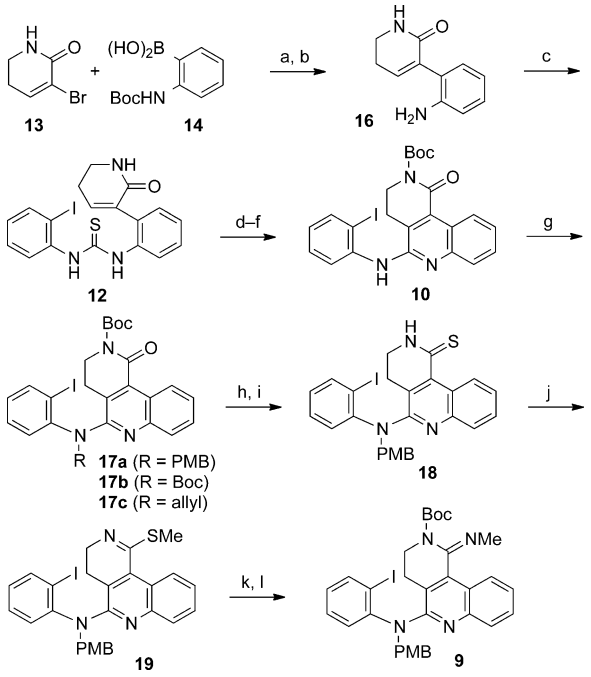


Scheme 2. Retrosynthetic analysis of **2**. Boc = *tert*-butoxycarbonyl, PMB = *para*-methoxybenzyl.



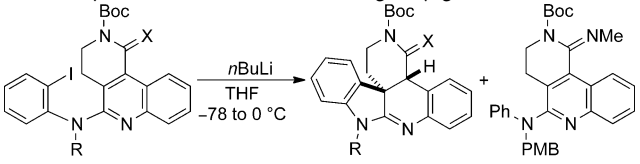
Scheme 3. Synthesis of substrates: a) $[PdCl_2(PPh_3)_2]$, Na_2CO_3, H_2O, dioxane, 100 °C, 88 %; b) trifluoroacetic acid (TFA), CH_2Cl_2, 0 °C, 99 %; c) 2-iodophenyl isothiocyanate (**15**), 4-dimethylaminopyridine (DMAP), toluene, 60 °C, 85 %; d) I_2, Et_3N, AcOEt, 0 °C; e) dichloroethane (DCE), 80 °C; f) Boc_2O, Et_3N, DMAP, THF, RT, 69 % (3 steps); g) for **17a**, PMBI, NaH, DMF, THF, 0 °C, 91 %; for **17b**, Boc_2O, DMAP, THF, RT, 92 %; for **17c**, allyl iodide, NaH, DMF, THF, 0 °C, 86 %; h) TFA, CH_2Cl_2, 0 °C, 99 %; i) Lawesson's reagent, toluene, 100 °C, 97 %; j) MeI, K_2CO_3, THF, RT, 89 %; k) $MeNH_2$, MeOH, 80 °C; l) Boc_2O, Et_3N, THF, RT, 87 % (2 steps).

Dearomatization is among the most attractive and efficient synthetic strategies, because it allows the facile synthesis of complex and multisubstituted carbocycles.[11] Among a diversity of dearomatizing synthetic methodologies, the nucleophilic addition of organometallic species, such as organolithium and organomagnesium, has been extensively studied.[11d,g,12] There are numerous examples of this type of addition reaction to aromatic systems having 10π electrons activated by electron-withdrawing groups, such as imines, amides, or oxazolines.[11d,13,14] However, only a single report has described the use of such reactions for the conversion of an electrophilic carbon into an all-carbon quaternary center.[13j]

The synthesis of substrates for the key dearomatizing conjugate addition of an in situ generated aryl anion is illustrated in Scheme 3. The Suzuki coupling reaction of the known α-bromolactam **13**[9] and boronic acid **14**[10] gave the lactam in 88 % yield, and the subsequent removal of the Boc group yielded aniline **16** in 99 % yield. Treatment of **16** with 2-iodophenyl isothiocyanate (**15**) afforded thiourea **12** in 85 % yield, which was converted into aminoquinoline **10** through a carbodiimide synthesis involving iodine-mediated desulfurization,[15] a thermal 6π electrocyclic reaction,[8] and selective Boc protection of the lactam nitrogen in 69 % overall yield for the three steps. Protection of the exocyclic nitrogen atom of aminoquinoline **10** with PMB iodide, Boc_2O, and allyl iodide gave **17a**, **17b**, and **17c** in 91 %, 92 %, and 86 % yield, respectively. The removal of the Boc group of **17a** afforded a deprotected amide in 99 % yield, and this amide was converted into thioamide **18** in 97 % yield by the reaction with Lawesson's reagent. Thioamide **18** was then methylated to form methyl thioimidate **19** in 89 % yield, and condensation with methylamine and the subsequent Boc protection of the resultant amidine afforded bisamidine **9** in 87 % overall yield for the two steps.

After the initial screening for the generation of the aryl anion from **17a** (see Table S1 in the Supporting Information), we examined the intramolecular conjugate addition of quinolinyl amides **17a–c** with *n*-butyl lithium (*n*BuLi; Table 1). Amide **17a** was treated with *n*BuLi (1.1 equiv) in THF at −78 °C, then the temperature was raised to 0 °C to give the desired product **20a** in 63 % yield (Table 1, entry 1).[16] The use of 2.1 equivalents of *n*BuLi slightly improved the yield to 68 % (Table 1, entry 2); however, neither Lewis acid ($BF_3{\cdot}Et_2O$ or $MgBr_2$) nor Lewis base (TMEDA or HMPA)[17] improved the yield or reaction rate.

Table 1: Optimization of the dearomatizing conjugate addition.



17a–c, 9 | 20a–c, 21 | 9'

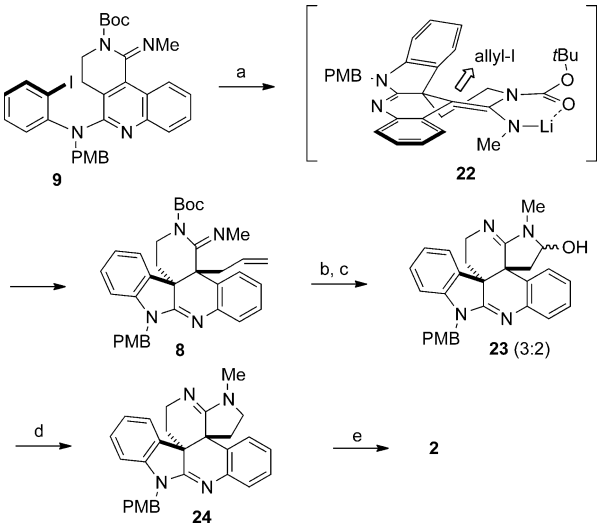
Entry	Substrates	*n*BuLi (equiv)	Yield [%]
1	**17a** (X = O, R = PMB)	1.1	63 (**20a**)
2	**17a** (X = O, R = PMB)	2.1	68 (**20a**)
3	**17b** (X = O, R = Boc)	1.1	0 (**20b**)
4	**17c** (X = O, R = allyl)	1.1	68 (**20c**)
5	**9** (X = NMe, R = PMB)	1.1	41 (**21**), 23 (**9′**)
6	**9** (X = NMe, R = PMB)	1.6	57 (**21**), 6 (**9′**)
7	**9** (X = NMe, R = PMB)	2.1	74 (**21**), trace (**9′**)

The role of the substituent (R) was investigated by subjecting the Boc adduct **17b** and the ally adduct **17c** to the same conditions as for entry 1 (Table 1, entries 3,4). The Boc group did not tolerate the conditions, although **17c** gave a product comparable to that obtained from **17a**. Since no differences were observed between the allyl and PMB derivatives, the iodobenzene rings of **17a** and **17c** might be positioned close to the quinoline ring in such a way that a facile intramolecular cyclization occurs, irrespective of the protecting group. The synthetic advantages of the PMB group urged us to use PMB amidine **9** as a substrate for further investigation.

We next focused on optimizing the reaction conditions for the dearomatization of quinolinyl amidine **9**. The conditions applied to **17a** were also applied to **9**, permitting the dearomatizing arylation to give the desired bisamidine **21** in 41% yield together with a significant amount of the deiodinated aminoquinoline **9'** as a byproduct (Table 1, entry 5). An increase in the amount of reagent did not significantly affect the yield in the case of **17a** (Table 1, entry 2); however, this adjustment improved the yield of **21**, resulting in 57% yield with 1.6 equivalents and 74% yield with 2.1 equivalents of *n*BuLi (Table 1, entries 6 and 7). Indeed, bisamidine **21** was obtained as a single diastereomer, and its structure was determined by X-ray crystallographic analysis, which revealed that the product had the desired perophoramidine-type relative configuration (see the Supporting Information). Based on these results, we selected **9** as a suitable substrate for the dearomatizing arylation and the subsequent transformations. The optimal conditions were determined to be those listed for entry 7.

Since azaenolate **22** was expected to be an intermediate during the last stage of the dearomatizing arylation, we envisioned the direct allylation of the intermediate in one pot (Scheme 4). When allyl iodide (2.1 equiv) was sequentially added after subjecting the substrate **9** to *n*BuLi, the allylated pentacyclic bisamidine **8** was successfully obtained in 67% yield as a single diastereomer.[18] To our knowledge, this is the first nucleophilic dearomatization of a 10π-electron aromatic system that enables the construction of two vicinal all-carbon quaternary centers. The relative configuration of the product **8** was established through the transformation of **8** into the final target **2**. The stereoselectivity of the reaction was attributed to steric congestion around the concave face of lithium azaenolate **22**, in agreement with the relevant results reported by the groups of Rainier and Weinreb.[3d,7]

The synthesis of **2** was completed through the construction of the A ring (Scheme 4). During the oxidative cleavage of the terminal olefin of **8** in two steps, the nucleophilic addition of the amidine resulted in the removal of the Boc group and the formation of hemiaminal **23** in 75% yield with a 3:2 diastereomeric ratio. Reduction of **23** with $NaCNBH_3$ gave hexacycle **24**, and its PMB group was removed by heating in H_3PO_4 and anisole[19] to afford **2** in 71% yield. The ^1H and ^{13}C NMR spectra of the TFA salt of **2** were identical to those described in the original report.[1] Without passing via an aminal intermediate, (±)-**2** was obtained from **13** in 17 steps with 9.5% overall yield, which is improved compared to the yield obtained in the synthesis described by Rainier and coworkers (18 steps, 7.5% overall yield).[7]



Scheme 4. Construction of vicinal quaternary centers and completion of the synthesis of **2**: a) *n*BuLi, THF, −78 to 0°C, then allyl iodide, 67% b) OsO_4, *N*-methyl morpholine *N*-oxide (NMO), acetone, RT; c) $NaIO_4$, $NaHCO_3$, THF, H_2O, RT, 75% (2 steps); d) $NaCNBH_3$, AcOH, MeOH, 0°C to 60°C, 76%; e) H_3PO_4, anisole, 120°C, 71%.

In summary, we first succeeded in the intramolecular dearomatizing arylation of electron-defficient quinolines bearing either an amide or an amidine by the lithium–iodine exchange method. The reaction was efficiently applied to the synthesis of (±)-dehaloperophoramidine **2** through a tandem dearomatizing arylation–allylation sequence, which consisted of an initial lithium–iodine exchange, a nucleophilic addition to the aminoquinolines, and a subsequent direct allylation of the resultant azaenolate. This reaction was remarkable for its efficient construction of a pentacyclic bisamidine bearing vicinal all-carbon quartenary centers.

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[1] S. M. Verbitski, C. L. Mayne, R. A. Davis, G. P. Concepcion, C. M. Ireland, *J. Org. Chem.* **2002**, *67*, 7124.
[2] a) A. Numata, C. Takahashi, Y. Ito, T. Takada, K. Kawai, Y. Usami, E. Matsumura, M. Imachi, T. Ito, T. Hasegawa, *Tetrahedron Lett.* **1993**, *34*, 2355; b) R. Jadulco, R. A. Edrada, R. Ebel, A. Berg, K. Schaumann, V. Wray, K. Steube, P. J. Proksch, *J. Nat. Prod.* **2004**, *67*, 78; c) H. Hayashi, H. Matsumoto, K. Akiyama, *Biosci. Biotechnol. Biochem.* **2004**, *68*, 753; d) P. W. Dalsgaard, J. W. Blunt, M. H. G. Munro, J. C. Frisvad, C. J. Christophersen, *J. Nat. Prod.* **2005**, *68*, 258.
[3] For synthetic studies of perophoramidine and related polycyclic amidines, see a) G. D. Artman III, S. M. Weinreb, *Org. Lett.* **2003**, *5*, 1523; b) J. Yang, H. Song, X. Xiao, J. Wang, Y. Qin, *Org. Lett.* **2006**, *8*, 2187; c) J. H. Seo, G. D. Artman III, S. M. Weinreb, *J. Org. Chem.* **2006**, *71*, 8891; d) M. A. Evans, J. R. Sacher, S. M. Weinreb, *Tetrahedron* **2009**, *65*, 6712; e) N. Voûte, D. Philp, A. M. Z. Slawin, N. J. Westwood, *Org. Biomol. Chem.* **2010**, *8*, 442; f) B. M. Trost, Y. Zhang, *Chem. Eur. J.* **2011**, *17*, 2916; g) H.

Wu, X. Xiao, Y. Qin, *Synlett* **2011**, *7*, 907; h) T. Ishida, C. Tsukano, Y. Takemoto, *Chem. Lett.* **2012**, *41*, 44; i) T. Ishida, Y. Takemoto, *Tetrahedron* **2013**, *69*, 4517.

[4] For synthetic studies of communesins and related polycyclic aminals, see a) J. A. May, R. K. Zeidan, B. M. Stoltz, *Tetrahedron Lett.* **2003**, *44*, 1203; b) S. L. Crawley, R. L. Funk, *Org. Lett.* **2003**, *5*, 3169; c) J. A. May, B. Stoltz, *Tetrahedron* **2006**, *62*, 5262; d) B. M. Trost, J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6314; e) S. L. Crawley, R. L. Funk, *Org. Lett.* **2006**, *8*, 3995; f) J. H. George, R. M. Adlington, *Synlett* **2008**, *14*, 2093; g) A. W. Schammel, B. W. Boal, L. Zu, T. Mesganaw, N. K. Garg, *Tetrahedron* **2010**, *66*, 4687; h) F. J. Robertson, B. D. Kenimer, J. Wu, *Tetrahedron* **2011**, *67*, 4327; i) A. W. Schammel, G. Chiou, N. K. Garg, *Org. Lett.* **2012**, *14*, 4556.

[5] a) J. R. Fuchs, R. L. Funk, *J. Am. Chem. Soc.* **2004**, *126*, 5068; b) H. Wu, F. Xue, X. Xiao, Y. Qin, *J. Am. Chem. Soc.* **2010**, *132*, 14052.

[6] a) J. Yang, H. Wu, L. Shen, Y. Qin, *J. Am. Chem. Soc.* **2007**, *129*, 13794; b) P. Liu, H. J. Seo, S. M. Weinreb, *Angew. Chem.* **2010**, *122*, 2044; *Angew. Chem. Int. Ed.* **2010**, *49*, 2000; c) Z. Zuo, W. Xie, D. Ma, *J. Am. Chem. Soc.* **2010**, *132*, 13226; d) Z. Zuo, D. Ma, *Angew. Chem.* **2011**, *123*, 12214; *Angew. Chem. Int. Ed.* **2011**, *50*, 12008; e) J. Belmar, R. L. Funk, *J. Am. Chem. Soc.* **2012**, *134*, 16941.

[7] A. Sabahi, A. Novikov, J. D. Rainier, *Angew. Chem.* **2006**, *118*, 4423; *Angew. Chem. Int. Ed.* **2006**, *45*, 4317.

[8] a) T. Saito, H. Ohmori, E. Furuno, S. Motoki, *Chem. Commun.* **1992**, 22; b) P. Molina, M. Alajarín, A. Vidal, P. Sánchez-Andrada, *J. Org. Chem.* **1992**, *57*, 929.

[9] M. G. Banwell, M. T. Jones, D. T. J. Loong, D. W. Lupton, D. M. Pinkerton, J. K. Ray, A. C. Willis, *Tetrahedron* **2010**, *66*, 9252.

[10] M. J. Sharp, W. Cheng, V. Snieckus, *Tetrahedron Lett.* **1987**, *28*, 5093.

[11] For recent reviews on dearomatizing reactions, see a) L. N. Mander, *Synlett* **1991**, 134; b) A. R. Pape, K. P. Kaliappan, E. P. Kündig, *Chem. Rev.* **2000**, *100*, 2917; c) A. I. Meyers, *J. Org. Chem.* **2005**, *70*, 6137; d) F. López-Ortiz, M. J. Iglesias, I. Fernández, C. M. Andújar-Sánchez, G. Ruiz-Gómez, *Chem. Rev.* **2007**, *107*, 1580; e) S. P. Roche, J. A. Porco Jr., *Angew. Chem.* **2011**, *123*, 4154; *Angew. Chem. Int. Ed.* **2011**, *50*, 4068; f) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem.* **2012**, *124*, 12834; *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; g) J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642.

[12] a) J. Clayden, C. J. Menet, D. J. Mansfield, *Org. Lett.* **2000**, *2*, 4229; b) J. Clayden, C. J. Menet, D. J. Mansfield, *Chem. Commun.* **2002**, 38; c) J. Clayden, S. D. Hamilton, R. T. Mohammaed, *Org. Lett.* **2005**, *7*, 3673; d) J. Clayden, S. Parris, N. Cabedo, A. H. Payne, *Angew. Chem.* **2008**, *120*, 5138; *Angew. Chem. Int. Ed.* **2008**, *47*, 5060; e) G. Ruiz-Gómez, A. Francesch, M. J. Iglesias, F. López-Ortiz, C. Cuevas, M. Serrano-Ruiz, *Org. Lett.* **2008**, *10*, 3981; f) G. Barbe, G. Pelletier, A. B. Charette, *Org. Lett.* **2009**, *11*, 3398.

[13] a) R. C. Fuson, K. D. Berlin, *J. Am. Chem. Soc.* **1959**, *81*, 2130; b) G. Bartoli, M. Basco, G. Baccolini, *J. Org. Chem.* **1980**, *45*, 2649; c) B. A. Barner, A. I. Meyers, *J. Am. Chem. Soc.* **1984**, *106*, 1865; d) A. I. Meyers, J. D. Brown, D. Laucher, *Tetrahedron Lett.* **1987**, *28*, 5279; e) K. Tomioka, M. Shindo, K. Koga, *J. Am. Chem. Soc.* **1989**, *111*, 8266; f) K. Maruoka, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1995**, *117*, 9091; g) A. Ahmed, J. Clayden, M. Rowley, *Chem. Commun.* **1998**, 297; h) J. Clayden, M. N. Kenworthy, *Org. Lett.* **2002**, *4*, 787; i) C. M. Andújar-Sánchez, J. Iglesias, F. López-Ortiz, *Tetrahedron Lett.* **2002**, *43*, 2565; j) L. Liu, Z. Wang, F. Zhao, Z. Xi, *J. Org. Chem.* **2007**, *72*, 3484.

[14] For other related dearomatizations of 10π-electron aromatic systems, see a) R. R. Goehring, Y. P. Sachdeva, J. S. Pisipati, M. C. Sleevi, J. F. Wolfe, *J. Am. Chem. Soc.* **1985**, *107*, 435; b) S. Quideau, M. A. Looney, L. Pouységu, *Org. Lett.* **1999**, *1*, 1651; c) M. Bao, H. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 759; d) Y. Yamaoka, H. Miyabe, Y. Takemoto, *J. Am. Chem. Soc.* **2007**, *129*, 6686; e) H. Iwasaki, T. Eguchi, N. Tsutsui, H. Ohno, T. Tanaka, *J. Org. Chem.* **2008**, *73*, 7145; f) J. García-Fortanet, F. Kessler, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 6676; g) B. Peng, X. Feng, X. Zhang, S. Zhang, M. Bao, *J. Org. Chem.* **2010**, *75*, 2619; h) R. B. Bedford, N. Fey, M. F. Haddow, R. F. Sankey, *Chem. Commun.* **2011**, *47*, 3649; i) K.-J. Wu, L.-X. Dai, S.-L. You, *Org. Lett.* **2012**, *14*, 3772; j) T. Shibuya, K. Noguchi, K. Tanaka, *Angew. Chem.* **2012**, *124*, 6323; *Angew. Chem. Int. Ed.* **2012**, *51*, 6219; k) A. Lin, J. Yang, M. Hashim, *Org. Lett.* **2013**, *15*, 1950.

[15] A. R. Ali, H. Ghosh, B. K. Patel, *Tetrahedron Lett.* **2010**, *51*, 1019.

[16] We have confirmed that the dearomatizing conjugate addition is applicable to similar substrates bearing a halogen atom. These results will be disclosed in the near future.

[17] We also investigated the effect of chiral ligands such as (−)-sparteine and (*R*,*R*)-1,2-diphenyl-1,2-dimethoxyethane, but no asymmetric induction was observed.

[18] While both direct C-allylation and [3,3]-sigmatropic rearrangement would be possible for the reaction pathway, we observed no N-allylated intermediate during the reaction. This result might support the former mechanism.

[19] F. Kienzle, A. Kaiser, M. S. Chodnekar, *Eur. J. Med. Chem.* **1982**, *17*, 547.

