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Polycyclic indoline derivatives by dearomatizing anionic cyclization of indole and tryptamine-derived ureas

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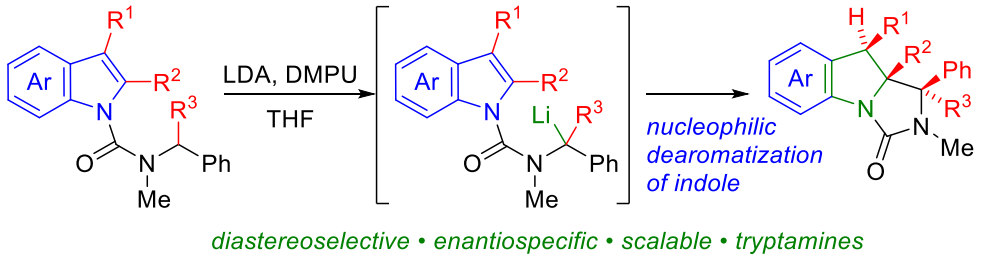
Supporting Information Placeholder



ABSTRACT: The base-promoted dearomatizing cyclization of anionic indole-containing urea derivatives provided tri- or tetracyclic indoline-containing scaffolds from lithiated urea intermediates. 3-Substituted indoles, including tryptamine derivatives, generally underwent the reaction in high yield and with excellent diastereoselectivity. In-situ IR spectroscopy suggests a deprotonation-carbolithiation-reprotonation mechanism.

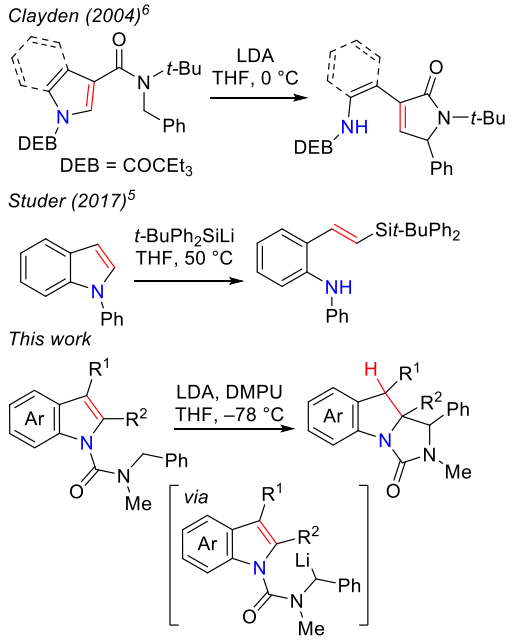
The amino acid tryptophan provides the starting material for the biosynthesis of a broad array of indole-derived secondary metabolites, many of them with valuable biological activity.[1] Not all contain the aromatic indole structure: a significant proportion of indole-derived alkaloids retain the indole connectivity, but are saturated in the five membered ring.[2] Synthetic approaches to these indoline-containing products commonly entail dearomatization of an indole precursor by electrophilic attack at the C-3 position, followed by nucleophilic addition into C-2 of the resulting iminum intermediate. Dearomatization is a powerful strategy for the synthesis of partially saturated heterocycles,[3] and recent work building upon this reactivity showed that the combination of a strong Lewis acid and a proton source could generate the iminum intermediate without C3-functionalization, resulting in dearomatizing C2-functionalization upon addition of an aryl nucleophile.[4]

By contrast, dearomatization reactions initiated by nucleophilic attack on the electron-rich indole ring are virtually unknown.[3a] Both Studer[5] and ourselves[6] have shown that attack on the C-2 position by a silyllithium or organolithium reagent results in ring opening to give products that no longer contain the indoline scaffold (Scheme 1). Indoles, pyrroles,[6] thiophenes and benzothiophenes[7] undergo comparable reactions, but for indoles the structural requirements for successful reactions are rather stringent: the bulky DEB protecting group was essential, for example. Likewise, Studer's silylation is limited to *N*-aryl indoles, and carbolithiation was unsuccessful with *n*-BuLi or *t*-BuLi. A general method for the nucleophilic dearomatization of *N*-protected indoles to provide polycyclic indoline-containing alkaloid-like structures is still lacking.

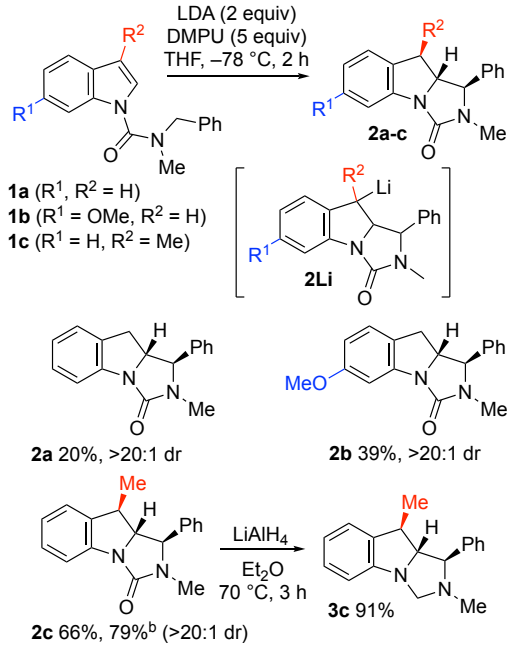
Recent work has shown that the carbonyl-directed lithiation of heterocyclic ureas provides fertile ground for the generation of new reactivity.[8] As part of this work, we explored the metallation of indole-derived N-benzyl ureas. Treating *N*-benzyl-*N*-methyl-*1H*-indole-1-carboxamide **1a** with 2 equiv of LDA in THF at –78 °C led to rapid decomposition to indole and other unidentified side-products. However, in the presence of 5 equiv of the lithium-coordinating co-solvent DMPU, full conversion was attained after 2 hours and the tricyclic indoline **2a** was obtained in 20% yield as a single diastereomer (Scheme 2). A similar reaction with the 6-methoxy indole **1b** provided a yield of 39% **2b**. Substitution of the 3-position of the indole starting material had an even more beneficial effect on the reaction. 3-Methylindole derivative **1c** reacted cleanly under the same conditions to give **2c** as a single diastereomer in 66% yield. Repeating the reaction on a 1 g scale further increased this yield to 79%, and treatment of the product with $LiAlH_4$ transformed it to the imidazolidine **3c**, indicating possible applications of this dearomatizing cyclization to the synthesis of polycyclic amines with alkaloid-like structures.

The success of these cyclizations suggested that the increased basicity of the organolithium intermediate **2Li** presumably generated by anionic cyclization may promote a cleaner reaction by favoring proton transfer from *i*-Pr_2NH (see mechanistic discussion below). We thus proceeded to develop further reactions of 3-substituted indoles.

Scheme 1. Nucleophilic dearomatization of indoles.



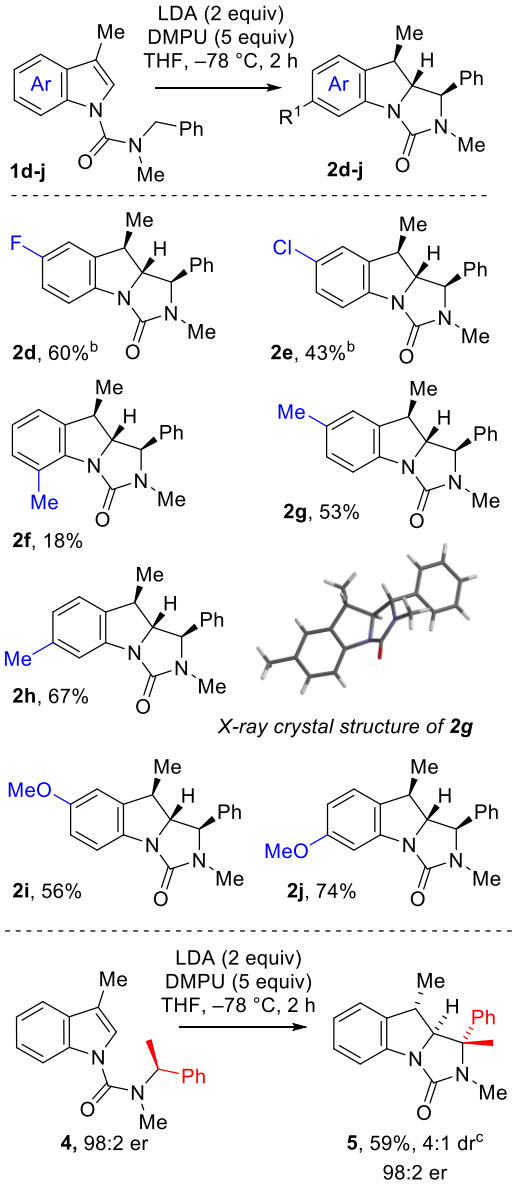
Scheme 2. Dearomatizing cyclization of indoles: initial results.



Footnotes: [a]Yield on 1 g scale

A further range of starting materials **1d-j** were made from their parent indoles by a Vilsmeier-Haack reaction followed by reduction with $LiAlH_4$ and N-acylation[9] (see Supporting Information). These new starting materials were subjected to the conditions (LDA, DMPU) used for **1a-c** (Scheme 3). 5-Fluoro and 5-chloro-substituted indoles cyclized successfully to give products **2d** and **2e**.[10] Similarly, substrates with methyl or methoxy groups at the 5 or 6 positions gave the dearomatised products in good yields (**2g-j**). In contrast, substitution at the 7-position was detrimental to the reaction, and the product **2f** (from 3,7-dimethylindole) was obtained in only 18% yield. All the products were obtained as essentially single diastereomers[11] with the X-ray crystal structure of **2g**,[12] supported by NOESY of **2c**, confirming relative stereochemistry in which the phenyl and methyl substituents occupy the *exo* face of the 5,5-fused bicyclic system.

Scheme 3. Cyclizations of 3-methylindole derivatives.[a]



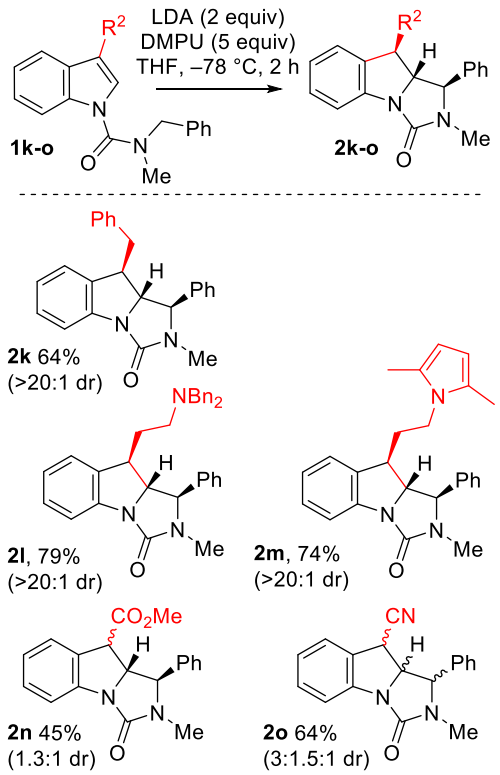
Footnotes: [a] > 20:1 dr unless otherwise stated. [b]10:1 dr. [c]Minor diastereoisomer has the opposite configuration at the two centers of the indoline ring.

A reaction performed on the related substrate **4** bearing an enantioenriched α-methylbenzyl substituent (98:2 er) also led to cyclization of the intermediate organolithium to a product **5** in 59% yield as a separable 4:1 mixture of diastereomers. The major diastereoisomer was formed without erosion of enantiomeric ratio, and presumably with retention of configuration,[13] indicating that the cyclization is faster than the racemization of the intermediate organolithium under the conditions of the reaction.[8f]

Alternative substituents at the 3-position were tolerated well (Scheme 4). The 3-benzyl-substituted indole **1k** gave a good yield of **2k** as a single diastereoisomer. The particular success of these

dearomatizing cyclizations of 3-alkylindoles suggested that tryptophan-derived ureas might also be suitable substrates, allowing the formation of alternatively connected tricyclic products.[14] Pleasingly, tryptamine derivatives **1l** and **1m** reacted cleanly to give the products **2l** and **2m** with dibenzyl and 2,6-dimethylpyrrole protecting groups.

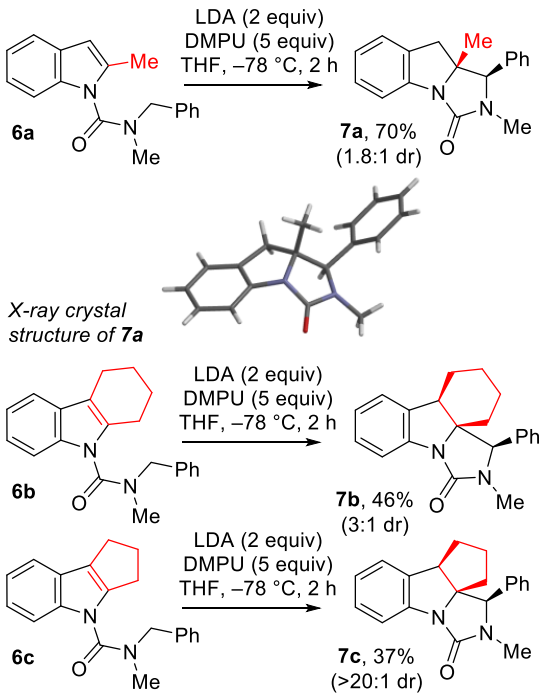
Scheme 4. Cyclizations of other 3-substituted indoles.



Similar cyclizations of **1n** and **1o** bearing electron-withdrawing groups at the 3-position also gave the products **2n** and **2o** in good yield. However, these reactions were much less diastereoselective, perhaps because the delocalized, planar product anion is protonated less diastereoselectively (see Scheme 6).

A final set of starting materials was made in which the 2-position of the indole was substituted. The first of these, the 2-methylindole derivative **6a**, cyclized in good yield under the standard conditions, although a mixture of diastereoisomers was obtained (Scheme 5; X-ray crystallography revealed the relative stereochemistry of the major diastereoisomer).[12,15] The fact that cyclization onto a substituted position was successful made possible the synthesis of a series of more elaborate tetracyclic products from ring-fused starting materials. Thus, tetrahydrocarbazole **6b** gave the tetracycle **7b** in 46% yield with a 3:1 diastereomeric ratio, while its 5-ring congener **6c** gave *cis*-**7c** in moderate yield with small amounts of the other diastereoisomer. The stereochemistry of the major isomers of **7b** and **7c** was confirmed by NOESY NMR analysis.

Scheme 5. 2-Substituted and tricyclic indole derivatives.

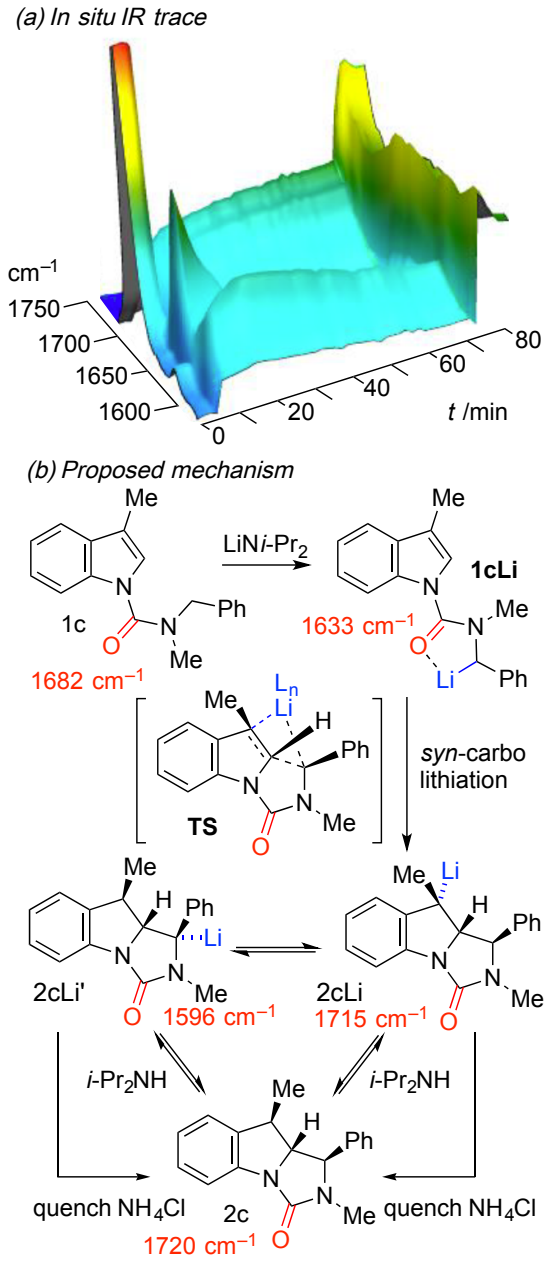


Some details of the mechanism of the cyclization of **1c** were revealed by in-situ infrared spectroscopy (Scheme 6).[16] To eliminate the obscuring effect of its urea carbonyl absorption, we performed the reaction in absence of DMPU. A solution of **1c** in THF showed a strong carbonyl absorption at 1682 cm^{-1}. Upon addition of 2 equiv LDA at –78 °C, this absorption was rapidly replaced by another carbonyl absorption at 1633 cm^{-1} corresponding to a transient species that we assume to be the lithiated starting material **1cLi**, possibly in a more complex solvated/aggregated state.[16b] Over a period of a few minutes this transient signal was replaced by three new absorptions at 1596, 1715 and 1720 cm^{-1} whose relative intensities changed over the remaining 70 min of the reaction, with the 1596 cm^{-1} signal decreasing while the other two increased. Quenching with aqueous ammonium chloride led to the disappearance of signals at 1596 and 1715 cm^{-1} and simultaneously intensified the signal at 1720 cm^{-1}. This signal was assigned to the product **2c** by comparison with the spectrum of the authentic sample, obtained in 52% yield after work-up and purification. We tentatively assign the structures **2cLi** and **2cLi'** to the absorptions at 1715 and 1596 cm^{-1}, respectively.[8b] These results point toward a mechanism that entails rapid benzylic lithiation followed by *syn*-carbolithiation of the indole ring. Slower equilibration then occurs by proton transfer between the diisopropylamine generated in the deprotonation step and the two alternative weakly acidic sites of the product.[17] Control over this equilibrium may be the reason why 3-substituents enhance the dearomatization reaction.

In summary, this intramolecular hydroalkylation reaction of lithiated indole-containing urea derivatives leads to heterocyclic indoline-containing polycyclic ring systems in a rare nucleophilic indole dearomatization reaction. The reactions proceed with high yields and excellent selectivity for 3-alkylated indole substrates, while other substitution patterns led to less predictable yields and selectivities. Substrates derived from tryptamine, as well as other biorelevant structures such as tricyclic indoles **6**, underwent the reaction. The reaction proved to be diastereoselective and (with enan-

tioenriched α-chiral organolithiums) enantiospecific, and the method has potential for the modular synthesis of modified indole alkaloid derivatives.

Scheme 6. *In-situ* IR investigation and postulated mechanism.[a]



Footnote: [a]Solvation or aggregation of the organolithium species is not shown but may be assumed.

Supporting Information

Full experimental data and NMR spectra of all new compounds.

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REFERENCES

1. (a) Seigler, D. S. *Plant secondary metabolism*; Springer: Boston, MA, 1998; p. 628. (b) Xu, W.; Gavia, D. J.; Tang, Y. *Nat. Prod. Rep.* **2014**, *31*, 1474. (c) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2015**, *32*, 1389.

2. Examples of such alkaloids are found in *Aspidosperma* and *Strychnos spp.*, as well as among pyrroloindoles, cyclotryptamines, communesines, and spiroindolines.

3. (a) *Dearomatising reactions using organo-lithiums*: Lemière, G.; Clayden, J. *Sci. Synth.*, **2011**; (b) Clayden, J.; Kenworthy, M. N.; Helliwell, M. *Orgh. Lett.* **2003**, *5*, 831; (c) Clayden, J.; Purewal, S.; Helliwell, M.; Mantell, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1049; (d) Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, I. *Tetrahedron Lett.* **2001**, *42*, 3411; (e) Clayden, J.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3059; (f) Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett.* **2005**, *7*, 3673.

4. (a) Nandi, R. K.; Ratsch, F.; Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Chem. Commun.* **2016**, *52*, 5328. (b) Morimoto, N.; Morioku, K.; Suzuki, H.; Takeuchi, Y.; Nishina, Y. *Org. Lett.* **2016**, *18*, 2020.

5. Xu, P.; Würthwein, E.-U.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2017**, *95*, 1527.

6. Clayden, J.; Turnbull, R.; Pinto, I. *Org. Lett.* **2004**, *6*, 609.

7. Clayden, J.; Turnbull, R.; Helliwell, M.; Pinto, I. *Chem. Commun.* **2004**, *21*, 2430.

8. (a) Hill, J. E.; Matlock, J. V.; Lefebvre, Q.; Cooper, K. G.; Clayden, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 5788. (b) Hall, J. E.; Matlock, J. V.; Ward, J. W.; Gray, K. V.; Clayden, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 11153. (c) Corbet, B. P.; Matlock, J. V.; Mas Roselló, J.; Clayden, J. *Comptes rendus - Chimie* **2017**, *20*, 634. (d) Tait, M. B.; Butterworth, S.; Clayden, J. *Org. Lett.* **2015**, *17*, 1236. (e) Maury, J.; Clayden, J. *J. Org. Chem.* **2015**, *80*, 10757. (f) Clayden, J.; Dufour, J.; Grainger, D. M.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488; (g) Tetlow, D. J.; Hennecke, U.; Raftery, J.; Waring, M. J.; Clarke, D. S.; Clayden, J. *Org. Lett.* **2010**, *12*, 5442; (h) Clayden J.; Donnard, M.; Lefranc, J.; Minassi, A.; Tetlow, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 6624; (i) Clayden, J.; Farnaby, W.; Grainger, D. M.; Hennecke, U.; Mancinelli, M.; Tetlow, D. J.; Hillier, I. H.; Vincent, M. A.; *J. Am. Chem. Soc.* **2009**, *131*, 3410.

9. Cheng, H.-G.; Lu, L.-Q.; Wang, T.; Yang, Q.-Q.; Liu, X.-P.; Li, Y.; Deng, Q.-H.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2013**, *52*, 3250.

10. A similar substrate containing a bromine atom completely decomposed under the reaction conditions, presumably due to competitive aryne generation.

11. For **2d** and **2e**, 10% of a minor diastereoisomer was obtained.

12. X-ray crystal data for **2g** and **7a** have been deposited with the CCDC: deposition numbers 1859678 and 1541914.

13. Vincent, M. A.; Maury, J.; Hillier, I. H.; Clayden, J. *Eur. J. Org. Chem.* **2015**, *5*, 953.

14. This method provides an unusual 6-5-5 tricyclic system, comparable to the ubiquitous 6-5-6 tricyclic system of tryptolines. For examples and relevance of such tricycles in medicinal chemistry, see: (a) Alagille, D.; Pfeiffer, B.; Scalbert, E.; Ferry, G.; Boutin, J. A.; Renard, P.; Viaud-Massuard, M.-C. *J. Enzyme. Inhib. Med. Chem.* **2004**, *19*, 137. (b) Chaulet, C.; Croix, C.; Alagille, D.; Normand, S.; Delwail, A.; Favot, L. Lecron, J.-C.; Viaud-Massuard, M.-C. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1019.

(c) Kong, W.-J.; Chen, X.; Wang, M.; Dai, H.-X.; Yu, J.-Q. *Org. Lett.* **2018**, *20*, 284.

15. Replacing the methyl by a phenyl group almost completely diverted the reaction to decomposition, giving the product in less than 10% yield.

16. (a) Atkinson, R. C.; Leonard, D. J.; Maury, J.; Castagnolo, D.; Volz, N.; Clayden, J. *Chem. Commun.* **2013**, 49, 9734. (b) Fournier, A. M.; Nichols, C. J.; Vincent, M. A.; Hillier, I. H.; Clayden, J. *Chem. Eur. J.* **2012**, *18*, 16478.

17. Deuterolysis of the reaction mixture did not give deuterated products, maybe because of rapid H/D exchange with *i*-Pr_2NH.