Organic LETTERS

Letter

pubs.acs.org/OrgLett

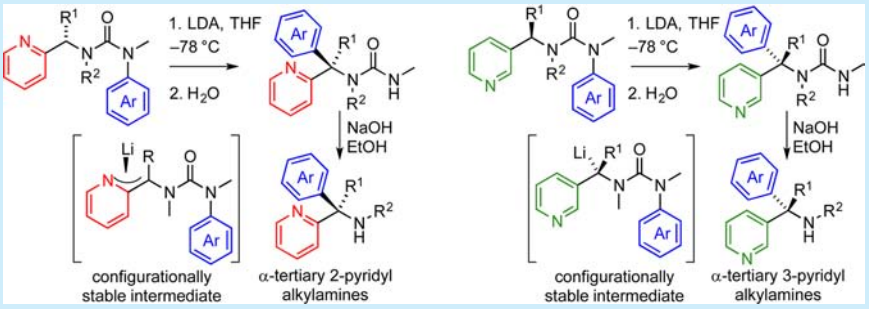
Stereospecific Intramolecular Arylation of 2- and 3-Pyridyl Substituted Alkylamines via Configurationally Stable α-Pyridyl Organolithiums

Julien Maury,[§,†,‡] Wojciech Zawodny,[§,†] and Jonathan Clayden*[,‡]

[†]School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, U.K.

[‡]School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K.

Supporting Information



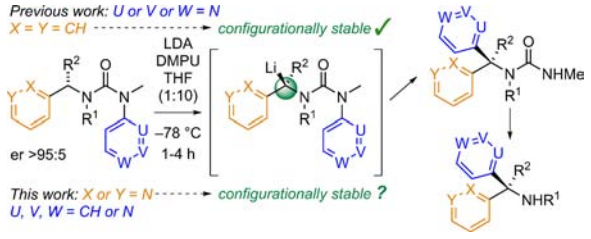
ABSTRACT: Treatment of *N*′-aryl urea derivatives of enantiomerically enriched α-(2-pyridyl) and α-(3-pyridyl)alkylamines with a base leads to the migration of the *N*′-aryl substituent from N to C in a 'nonclassical' intramolecular nucleophilic aromatic substitution reaction. Both electron-rich and -poor rings migrate successfully. A new quaternary stereogenic center is formed adjacent to the pyridine ring with high stereospecificity, even when the intermediate anion is a presumably planar 2-picolyllithium. Base hydrolysis of the urea gives enantiomerically enriched α-pyridylalkylamines.

Pyridines play a vital role in medicinal chemistry,[1] being the most common heterocyclic ring encountered in small molecule drugs.[2] Substituted chiral pyridines with a stereogenic center at the 'picolinic' position α to the pyridine ring are present in many biologically active molecules[3] and chiral ligands.[4] More specifically, congested quaternary stereogenic centers bearing both pyridine and phenyl rings are present in antihistamines such as pheniramine[5] and doxylamine[6] and in potent cholesteryl ester transfer protein (CETP) inhibitors.[7]

Methods for the synthesis of α-chiral amines bearing a pyridine ring at the stereogenic center typically rely on auxiliaries to direct addition to, or reduction of, an intermediate imine.[8] For enantiopure α-tertiary amines with a pyridine ring as one of the substituents at the quaternary stereogenic center synthetic approaches are very limited.[9] We previously reported a stereospecific route to a subclass of these structures by intramolecular migration of pyridine rings to the α-position of lithiated urea derivatives of *N*-α-methylbenzylamine, giving α-tertiary amines after the solvolysis of the urea (Scheme 1).[9c] Stereospecificity is ensured by the configurational stability of the benzyllithium intermediates[10] on the time scale of the rearrangement reaction.[11]

We now report a complementary method for the generation of pyridine-bearing quaternary stereogenic centers by stereospecific intramolecular arylation[12] α to 2- or 3-pyridyl substituents. The reaction is mediated by pyridine-stabilized organolithiums that exhibit remarkable configurational stability, given the electron-withdrawing, anion-stabilizing nature of the pyridyl substituents.

Scheme 1. α-Pyridylation of Chiral Amines[2]

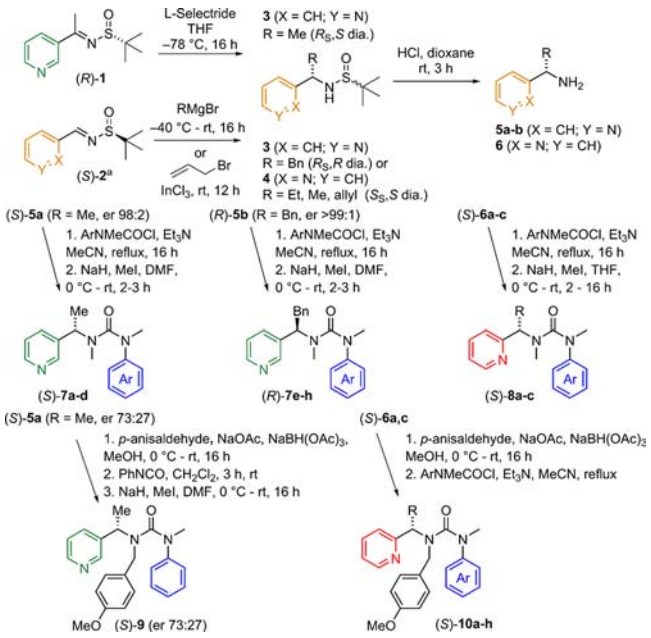


Chiral amine precursors **5** and **6** bearing an amino group and a 3- or 2-pyridyl substituent at the stereogenic center were made using Ellman's *N*-sulfinyl auxiliary.[8] Grignard addition[13] and indium allylation[14] of *N*-sulfinyl aldimines **2** or diastereoselective reduction of *N*-sulfinyl ketimines[15] **1** gave highly enantioenriched sulfinamides **3** and **4** that were hydrolyzed to chiral primary amines **5** and **6** (Scheme 2). The amines were either acylated (with *N*-methylcarbamoyl chlorides) and methylated or reductively aminated with *p*-methoxylbenzaldehyde and acylated (with aryl isocyanates, followed by methylation, or with *N*-methyl-

Received: December 6, 2016
Published: January 18, 2017

DOI: 10.1021/acs.orglett.6b03603
Org. Lett. 2017, 19, 472–475

Scheme 2. Synthesis of Enantioenriched 2- and 3-Pyridyl-Substituted Urea Starting Materials

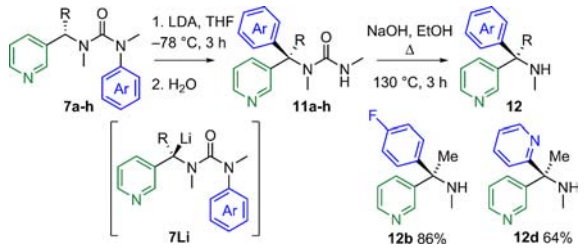


[a]Enantiomeric sulfinimine (*R*)-**2** was used for the synthesis of (*R*)-**5b**.

carbamoyl chlorides), giving ureas **7**–**10** as starting materials for organolithium-mediated rearrangements.

The 3-pyridyl-substituted urea **7a** (R = Me, Ar = Ph) was treated with LDA in THF at −78 °C (Scheme 3). After 3 h, the

Scheme 3. Stereospecific Intramolecular Arylation of 3-Pyridine-Substituted Ureas[a]



[a]For simplicity, reactions of the *S* enantiomers are shown; in the case of **7e**–**h** the *R* enantiomer was used (see Table 1).

reaction was quenched, and rearranged urea **11a**, in which the phenyl group had migrated from nitrogen to the position α to the pyridyl ring, was isolated in good yield without loss of enantiomeric purity (Table 1, entry 1). No additives[16] were required to maintain the stereospecificity[17] of the reaction, indicating that the presumed intermediate 3-pyridine-stabilized organolithium **7Li** does not racemize on the time scale of the rearrangement. The electron-deficient *para*-fluorophenyl, *para*-chlorophenyl, and 2-pyridyl rings of **7b**–**d** likewise migrated to give **11b**–**d** in good yields, again with full stereospecificity (entries 2–4). Urea **11d**, formed in 98:2 er, provides the first example of an α-tertiary amine derivative with both a 2- and a 3-pyridyl substituent at the stereogenic center. The tolerance of the reaction to steric hindrance[18] was explored by replacing the α-methyl substituent with a benzyl group (entries 5–8). The rearrangements of **7e**–**7h** were fully stereospecific, and **11e** and **11h** were formed in good yields.

Table 1. Arylation of 3-Pyridine-Substituted Ureas

entry	SM, er[a]	R	Ar	product, yield (%)	product, er[a]
1	(*S*)-**7a** 98:2	Me	C_6H_5	(*R*)-**11a** 65	98:2
2	(*S*)-**7b** 98:2	Me	4-FC_6H_4	(*R*)-**11b** 74	98:2
3	(*S*)-**7c** 98:2	Me	4-ClC_6H_4	(*R*)-**11c** 63	98:2
4	(*S*)-**7d** 98:2	Me	2-pyridyl	(*S*)-**11d** 76	98:2
5	(*R*)-**7e** >99:1	Bn	C_6H_5	(*S*)-**11e** 87	>99:1
6	(*R*)-**7f** >99:1	Bn	3-ClC_6H_4	(*S*)-**11f** 22	>99:1
7	(*R*)-**7g** >99:1	Bn	3-$MeOC_6H_4$	(*S*)-**11g** 26	>99:1
8	(*R*)-**7h** >99:1	Bn	2-pyridyl	(*R*)-**11h** 88	>99:1

[a]Enantiomeric ratio by HPLC on chiral stationary phase.

Hydrolysis of the rearranged products under basic conditions cleaved the urea in good yield to provide α-tertiary amines **12**, illustrated by the formation of **12b** and **12d** (Scheme 3).

The absolute configuration of (*R*)-**11c** was determined by means of X-ray crystallography (Figure 1) and confirmed that the rearrangements of 3-pyridyl ureas proceed with retention of configuration, as has been observed in previous related rearrangements.[11]

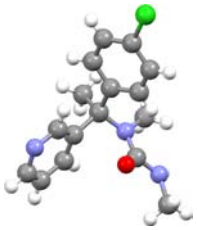
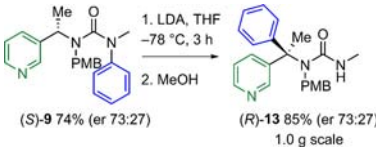


Figure 1. X-ray crystal structure of (*R*)-**11c**.

Replacing the *N*-methyl substituent with an *N*-*p*-methoxybenzyl (PMB) protecting group had no effect on the stereospecificity of the reaction: samples of (*S*)-**9** rearranged to urea **13** in good yield without loss of er on both 200 mg and 1 g scales (Scheme 4).

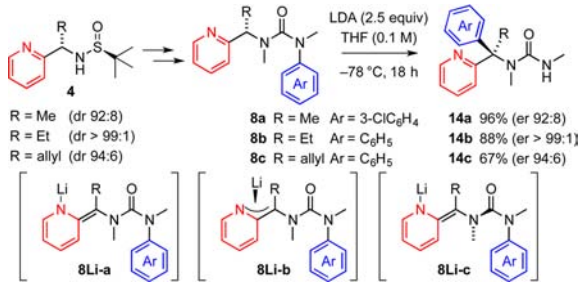
Scheme 4. Stereospecific Intramolecular Arylation of an Amine with a PMB (*p*-Methoxybenzyl) Protecting Group



2-Pyridyl-substituted organolithiums (2-picolyllithiums) have structures best characterized as azaenolates, as represented in Scheme 5 as **8Li-a**, with a planar α-carbon and the negative charge located principally at nitrogen.[19] Urea-substituted enolates possessing other stereogenic centers undergo diastereoselective intramolecular arylation,[20] but (except for examples with special structural features promoting chiral memory by hindered rotation[21]) without stereospecificity at the planar enolate carbon atom.[22] Nonetheless, treatment of the 2-pyridylurea **8a** with LDA in THF gave the rearranged compound **14a** with the same er (92:8) as the starting material (Scheme 5). Similarly, there was no loss of er in the rearrangements of ureas **8b** and **8c**: product ureas **14b** and **14c** were obtained in good yield and er (88%, 99:1 er and 67%, 94:6 er).

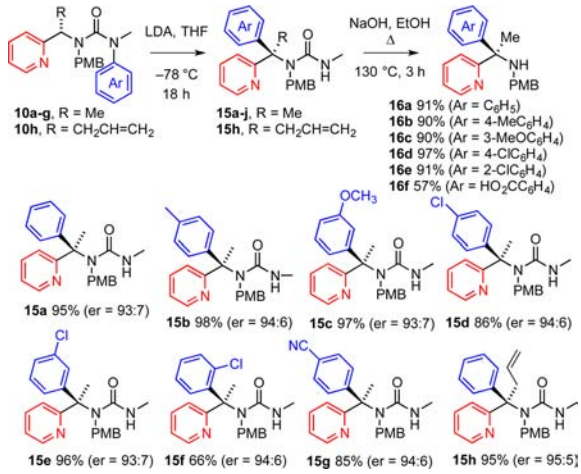
DOI: 10.1021/acs.orglett.6b03603
Org. Lett. 2017, 19, 472–475

Scheme 5. Stereospecific Aryl Migration within 2-Pyridyl-Stabilized Anions



The stereospecificity of the α-(2-pyridyl)alkylamine synthesis was exploited by rearrangement of a range of *p*-methoxybenzyl-protected ureas **10a–h** built from chiral 2-pyridylamines (Scheme 6) to products **15a–h** without erosion of enantiomeric

Scheme 6. Synthesis of Protected Tertiary α-(2-Pyridyl)benzylamines by Stereospecific Intramolecular Arylation (PMB = *p*-methoxybenzyl)



enrichment. Migrating rings with either electron-donating or -withdrawing substituents at the *para* and *meta* positions all rearranged in high yield (85–98%) and good er (94:6–93:7) (**15b–15e**, **15g**). The migration of aromatic groups substituted at the *ortho* position gave lower yields with 2-chlorophenylurea **10f**; the reaction remained stereospecific, but the yield dropped to 66%. Attempted rearrangement of a 1-naphthyl-substituent failed. Hydrolysis of the ureas **15** under basic conditions (NaOH, EtOH) gave the valuable 2-pyridyl substituted α-tertiary amines **16** in high yields (Scheme 6).[23]

We assume that in the rearrangements of ureas **7–10** the reaction mechanism proceeds by selective deprotonation of the acidic "picolinic" position α to the pyridyl ring to give an anionic species **7–10Li**, which undergoes the conformational reorganization required to attack the aryl ring borne by the other nitrogen atom, but without loss of configurational integrity. A nonclassical intramolecular S_NAr reaction[11b] leads to the product anion, which is protonated on workup. The intermediate anionic species **7–10Li** must retain their absolute stereochemistry on the time scale of the rearrangement. This stereospecificity is a feature of the reaction shared with other related rearrangements of lithiated ureas[9c,11a,24] (along with thiocarbamates[25] and, to a lesser extent, carbamates[16,26]), though not the cyclic ureas so far explored.[27]

The structure of 3-picolyllithiums related to **7Li** and **9Li** have not been examined in detail, but the inability of the nitrogen atom at the 3-position to stabilize the negative charge by delocalization suggests they may have structural similarities with configurationally stable α-nitrogen substituted benzyllithiums.[3] By contrast, computational and crystallographic studies of 2-picolyllithiums related to **8Li** and **10Li**, whose negative charge is stabilized by delocalization onto the pyridyl nitrogen, show that the negative charge is principally located at the nitrogen atom, and the anion may be interpreted as a planar azaenolate, i.e. **8Li-a** (Scheme 5).[19] Given the probable planarity of the α-carbon of the intermediate anion **8Li**, possible mechanisms for stereospecificity include long-lived planar chirality within an intermediate pyridyllithium species **8Li-b** (Scheme 5)[25b,c,28] or the adoption by the urea of a chiral, twisted conformation (such as **8Li-c**) that rearranges to product faster than it can relax to an enantiomeric mixture of conformers.[21,29]

To gain deeper insight into the mechanism of the reaction, the conversion of **8b** to **14b** in THF at –78 °C was followed by *in situ* infrared spectroscopy (React-IR) (Figure 2 and Scheme 7). In

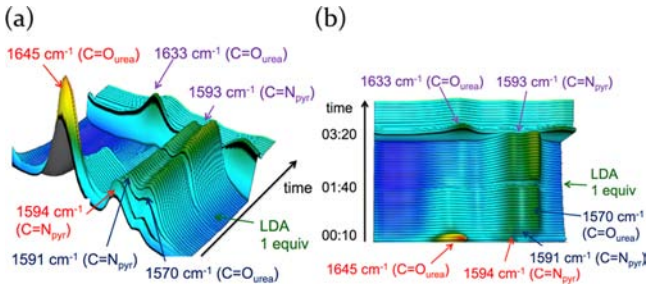
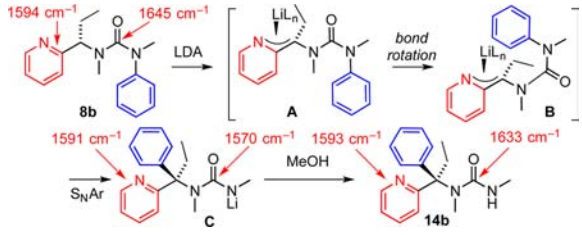


Figure 2. In situ infrared study of the rearrangement of **8b** to **11b** (00:10:00, addition of 2.5 equiv of LDA starts; 01:40:00, addition of 1 equiv of LDA complete; 03:30:00, reaction quenched with MeOH).

Scheme 7. Proposed Mechanistic Pathway from 8b to 14b



THF at –78 °C, IR shows one C=O stretching absorption at 1645 cm^{-1} and one pyridine C=N stretching absorption at 1594 cm^{-1} (Figure 2a). After 10 min (00:10) an initial 2.5 equiv of LDA was added, causing the C=O stretch at 1645 cm^{-1} to diminish, the pyridine stretch to shift to 1591 cm^{-1}, and a new C=O stretch to grow at 1570 cm^{-1}. We assign these peaks to the rearranged, lithiated urea **C**.[11a,30] Adding another equivalent of LDA 90 min later (01:40) completes the reaction, as indicated by the disappearance of the C=O stretch (starting material **A**) at 1645 cm^{-1} and a further increase of the C=O stretch (lithiated product **C**) at 1570 cm^{-1}. The detailed mechanism of formation of **C** from **B** was not explored, but previous studies[11b] have suggested that related reactions proceed by a partially concerted S_NAr reaction. Finally (Figure 2b) addition of MeOH (03:20) protonates the urea anion of **C** to give **14b**, with a urea C=O stretch at 1633 cm^{-1}. No species identifiable as lithiated starting material **A** was observed. Product **14b** was recovered in 89% yield.

DOI: 10.1021/acs.orglett.6b03603
Org. Lett. 2017, 19, 472–475

In summary, both α-(2-pyridyl) and α-(3-pyridyl) alkylamines may be arylated with total enantiospecificity at their α-position by intramolecular migration of an aryl substituent within their lithiated *N*′-aryl urea derivatives. Despite their delocalized structure, the intermediate 2-pyridyl-substituted anions are configurational stable on the time scale of the rearrangement.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03603.

Full details of experimental procedures, characterization data, and spectra of all new compounds (PDF)
Crystallographic data for (*R*)-**11c** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: j.clayden@bristol.ac.uk.

ORCID

Jonathan Clayden: 0000-0001-5080-9535

Author Contributions

§J.M. and W.Z. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the EU (Marie Curie IEF ENOLAR) and by the BBSRC. We thank Dr. James Raftery (University of Manchester) for determining the X-ray crystal structure of (*R*)-**11c**.

■ REFERENCES

(1) (a) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (c) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

(2) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845.

(3) (a) Ullrich, T.; Krich, S.; Binder, D.; Mereiter, K.; Anderson, D. J.; Meyer, M. D.; Pyerin, M. *J. Med. Chem.* **2002**, *45*, 4047. (b) Lawson, E. C.; Hoekstra, W. J.; Addo, M. F.; Andrade-Gordon, P.; Damiano, B. P.; Kauffman, J. A.; Mitchell, J. A.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2619. (c) Husain, I.; Saquib, M.; Bajpai, V.; Kumar, B.; Shaw, A. K. *J. Org. Chem.* **2011**, *76*, 8930. (d) Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685. (e) Nicolaou, K. C.; Safina, B. S.; Zak, M.; Lee, S. H.; Nevalainen, M.; Bella, M.; Estrada, A. A.; Funke, C.; Zécri, F. J.; Bulat, S. *J. Am. Chem. Soc.* **2005**, *127*, 11159.

(4) (a) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297. (b) Brunner, H.; Niemetz, M. *Monatsh. Chem.* **2002**, *133*, 115. (c) Chelucci, G.; Pinna, G. A.; Saba, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2571. (d) Canary, J. W.; Allen, C. S.; Castagnetto, J. M.; Wang, Y. *J. Am. Chem. Soc.* **1995**, *117*, 8484. (e) Chelucci, G.; Conti, S.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1991**, *47*, 8251. (f) Brunner, H.; Fisch, H. *J. Organomet. Chem.* **1987**, *335*, 15. (g) Zai, S.; Gao, H.; Huang, Z.; Hu, H.; Wu, H.; Wu, Q. *ACS Catal.* **2012**, *2*, 433. (h) Baratta, W.; Benedetti, F.; Del Zotto, A.; Fanfoni, L.; Felluga, F.; Magnolia, S.; Putignano, E.; Rigo, P. *Organometallics* **2010**, *29*, 3563.

(5) Nguyen, T.; Shapiro, D. A.; George, S. R.; Setola, V.; Lee, D. K.; Cheng, R.; Rauser, L.; Lee, S. P.; Lynch, K. R.; Roth, B. L.; O'Dowd, B. F. *Mol. Pharmacol.* **2001**, *59*, 427.

(6) Eccles, R.; van Cauwenberge, P.; Tetzloff, W.; Borum, P. *J. Pharm. Pharmacol.* **1995**, *47*, 990.

(7) Harikrishnan, L. S.; Finlay, H. J.; Qiao, J. X.; Kamau, M. G.; Jiang, J.; Wang, T. C.; Li, J.; Cooper, C. B.; Poss, M. A.; Adam, L. P.; Taylor, D. S.; Chen, A. Y. A.; Yin, X.; Sleph, P. G.; Yang, R. Z.; Sitkoff, D. F.; Galella, M. A.; Nirschl, D. S.; Van Kirk, K.; Miller, A. V.; Huang, C. S.; Chang, M.; Chen, X. Q.; Salvati, M. E.; Wexler, R. R.; Lawrence, R. M. *J. Med. Chem.* **2012**, *55*, 6162.

(8) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(9) (a) Shaw, A. W.; deSolms, S. J. *Tetrahedron Lett.* **2001**, *42*, 7173. (b) Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* **1997**, *62*, 5537. (c) Clayden, J.; Hennecke, U. *Org. Lett.* **2008**, *10*, 3567.

(10) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002.

(11) (a) Clayden, J.; Dufour, J.; Grainger, D. M.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488. (b) Vincent, M. A.; Maury, J.; Hillier, I. H.; Clayden, J. *Eur. J. Org. Chem.* **2015**, *2015*, 953.

(12) Clayden, J. In *Lithium Compounds in Organic Synthesis*; Luisi, R., Capriati, V., Eds.; Dearomatization and Aryl Migration in Lithium Chemistry; 2014.

(13) Prasad, K. R.; Revu, O. *Tetrahedron* **2013**, *69*, 8422.

(14) Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259.

(15) Chelucci, G.; Baldino, S.; Chessa, S.; Pinna, G. A.; Soccolini, F. *Tetrahedron: Asymmetry* **2006**, *17*, 3163.

(16) Fournier, A. M.; Brown, R. A.; Farnaby, W.; Miyatake-Ondozabal, H.; Clayden, J. *Org. Lett.* **2010**, *12*, 2222.

(17) Zimmerman, H. E.; Singer, L.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1959**, *81*, 108.

(18) Clayden, J.; Donnard, M.; Lefranc, J.; Minassi, A.; Tetlow, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 6624.

(19) (a) Wiklund, T.; Olsson, S.; Lennartson, A. *Monatsh. Chem.* **2011**, *142*, 813. (b) Pratt, L. M.; Khan, I. M. *J. Mol. Struct.: THEOCHEM* **1996**, *367*, 33. (c) Ott, H.; Pieper, U.; Leusser, D.; Flierler, U.; Henn, J.; Stalke, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 2978. (d) Pieper, U.; Stalke, D. *Organometallics* **1993**, *12*, 1201.

(20) (a) Maury, J.; Clayden, J. *J. Org. Chem.* **2015**, *80*, 10757. (b) Atkinson, R. C.; Fernández-Nieto, F.; Mas Roselló, J.; Clayden, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 8961.

(21) Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T. *J. Am. Chem. Soc.* **2013**, *135*, 13294.

(22) Atkinson, R. C.; Leonard, D. J.; Maury, J.; Castagnolo, D.; Volz, N.; Clayden, J. *Chem. Commun.* **2013**, *49*, 9734.

(23) The er of amines **16a-f**, like those of **12b,d** was not determined, but was assumed to be the same as the parent urea.

(24) Tait, M.; Donnard, M.; Minassi, A.; Lefranc, J.; Bechi, B.; Carbone, G.; O'Brien, P.; Clayden, J. *Org. Lett.* **2013**, *15*, 34.

(25) (a) MacLellan, P.; Clayden, J. *Chem. Commun.* **2011**, *47*, 3395. (b) Mingat, G.; MacLellan, P.; Laars, M.; Clayden, J. *Org. Lett.* **2014**, *16*, 1252. (c) Mingat, G.; McDouall, J. J. W.; Clayden, J. *Chem. Commun.* **2014**, *50*, 6754.

(26) 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.

(27) (a) Bach, R.; Clayden, J.; Hennecke, U. *Synlett* **2009**, *2009*, 421. (b) Tait, M. B.; Ottersbach, P. A.; Tetlow, D. J.; Clayden, J. *Org. Process Res. Dev.* **2014**, *18*, 1245. (c) Tait, M. B.; Butterworth, S.; Clayden, J. *Org. Lett.* **2015**, *17*, 1236.

(28) (a) Tetlow, D. J.; Hennecke, U.; Raftery, J.; Waring, M. J.; Clarke, D. S.; Clayden, J. *Org. Lett.* **2010**, *12*, 5442. (b) Tetlow, D. J.; Vincent, M. A.; Hillier, I. H.; Clayden, J. *Chem. Commun.* **2013**, *49*, 1548.

(29) Clayden, J.; Stimson, C. C.; Keenan, M.; Wheatley, A. E. H. *Chem. Commun.* **2004**, *2*, 228.

(30) (a) Grainger, D. M.; Smith, A. C.; Vincent, M. A.; Hillier, I. H.; Wheatley, A. E. H.; Clayden, J. *Eur. J. Org. Chem.* **2012**, *2012*, 731. (b) Lefranc, J.; Fournier, A. M.; Mingat, G.; Herbert, S.; Marcelli, T.; Clayden, J. *J. Am. Chem. Soc.* **2012**, *134*, 7286.

DOI: 10.1021/acs.orglett.6b03603
Org. Lett. 2017, 19, 472−475