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Intramolecular Vinylation of Secondary and Tertiary Organolithiums

Julien Lefranc,[†] Anne M. Fournier,[†] Gaëlle Mingat,[†] Simon Herbert,[†] Tommaso Marcelli,[†,‡] and Jonathan Clayden*[,†]

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

[‡]Dipartimento di Chimica, Materiali e Ingegneria Chimica "Giulio Natta", Politecnico di Milano, via Mancinelli 7, 20131 Milano, Italy

Supporting Information

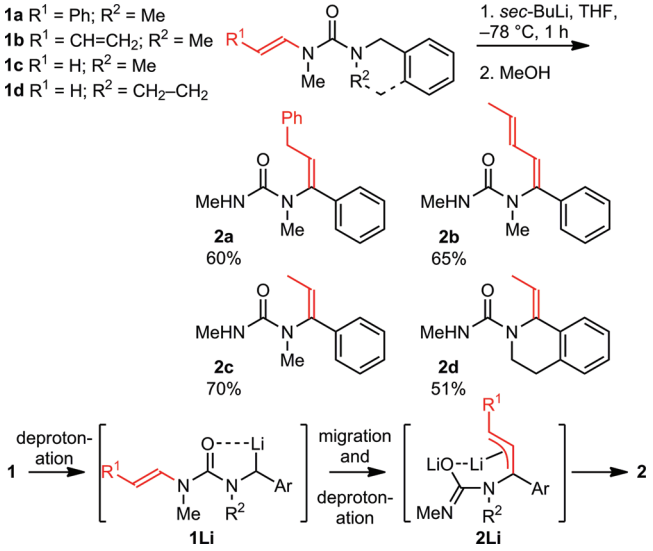
ABSTRACT: Deprotonation of benzylic ureas, carbamates, and thiocarbamates bearing *N*′-alkenyl substituents generates carbanions which undergo intramolecular migration of the alkenyl group to the carbanionic center. Solvolysis of the urea products generates α-alkenylated amines. With an enantiomerically pure starting urea, migration proceeds stereospecifically, generating in enantiomerically enriched form products containing allylic quaternary stereogenic centers bearing N. Computational and *in situ* IR studies suggest that the reaction, formally a nucleophilic substitution at an sp^2 carbon atom, proceeds by a concerted addition-elimination pathway.

Many classes of electrophiles, including alkylating and acylating agents, carbonyl compounds, and halogenating agents, are compatible with organolithium chemistry.[1] However, the direct arylation of organolithiums is a particular challenge typically overcome by transmetalation with Cu or Zn[2,3] or by intramolecular aryl transfer.[4−7] Vinylic electrophiles likewise cannot normally be coupled directly with organolithiums, and transmetalation is usually required to form new vinylic C−C bonds.[2d-f]

In this paper we present a new approach to the vinylation of organolithium nucleophiles that allows new C−C bonds to be formed by nucleophilic attack even on unactivated alkenes and permits the stereospecific construction of functionalized quaternary centers by vinylation of tertiary carbanions. We had previously shown that when ureas[5] or carbamates[6] bearing *N*′-aryl groups are lithiated, nucleophilic substitution at the *ipso* position of the aryl group leads to intramolecular transfer of the aryl substituent to the carbanion center.[8] Given that this intramolecular nucleophilic aromatic substitution is successful even with electron-rich rings,[5a] it seemed plausible that the migration of electron-rich alkenyl groups might also be feasible.

In preliminary experiments, *N*-benzyl-*N*-alkenyl ureas **1** were made in three steps from commercially available starting materials.[9] Styrenyl urea **1a** was treated with *sec*-BuLi (2 equiv) at −78 °C in THF and allowed to stir for 1 h before quenching with MeOH (Scheme 1). Workup and purification yielded a single *Z* geometrical isomer of the rearranged urea **2a** in 60% yield. We presume the reaction proceeds through deprotonation of the urea α to N[5a] to give the benzyllithium **1Li**, followed by migration of the styrenyl group to the carbanionic center. A second deprotonation α to N would give a *Z*-configured O-chelated cinnamyllithium **2Li**,[5d] which is quenched at its γ-position, providing **2a**. A similar rearranged product **2b** was obtained from butadienyl urea **1b**. Remarkably, even the simple vinyl urea **1c** underwent rearrangement, forming the ethylidene-substituted **2c** as its *Z* isomer. Likewise, vinyl migration provided the *Z*-ethylidene substituted urea **2d** from *N*-vinyl tetrahydroisoquinolinyl urea **1d**.

Scheme 1. Alkylidenation of Benzylic Ureas by Lithiation and Rearrangement



The second deprotonation (leading to **2Li**) would be avoided in any similar vinylation of *tertiary* carbanions[10] because those products would lack a further proton at the carbanion center. α-Alkylbenzylamine derivatives **3** (X = NH) were converted into the *N*-vinyl ureas **4** by reaction with commercially available vinyl isocyanate and, where necessary, *N*-methylation (full details are provided in the Supporting Information (SI)). When **4a** (Ar = Ph, R^1 = Me) was treated with *sec*-BuLi in THF under the conditions reported in Scheme 1, only starting material was recovered. We have previously noted that the lithium-coordinating cosolvent DMPU markedly increases the reactivity of hindered organolithiums toward nucleophilic attack on arenes and alkenes,[5a,e] probably by favoring the formation of solvent-separated ion pairs.[11] On repeating the rearrangement of **4a** using 10% DMPU as a cosolvent the rearranged derivative **7a** of a tertiary allylic amine

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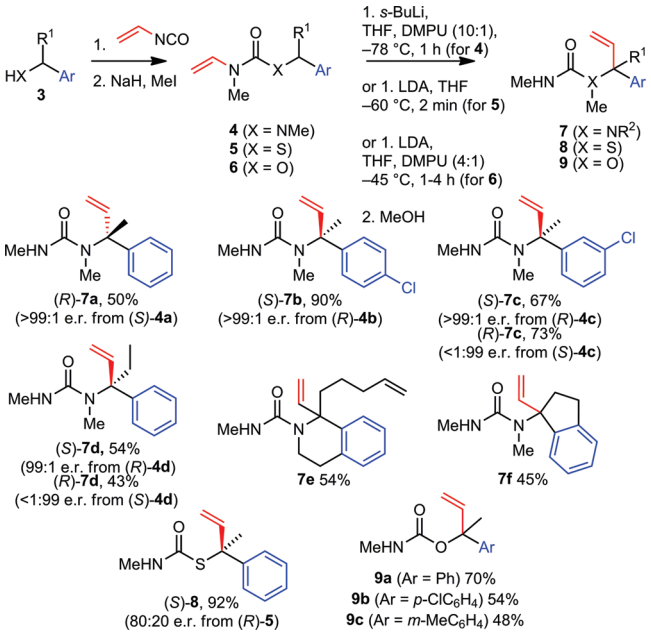
was obtained (Scheme 2), and when the rearrangement was performed using an enantiomerically pure starting urea (*S*)-**4a**

Scheme 2. Vinylation of Organolithiums α to N, O, or S from α-Methylbenzyl Amine[a]



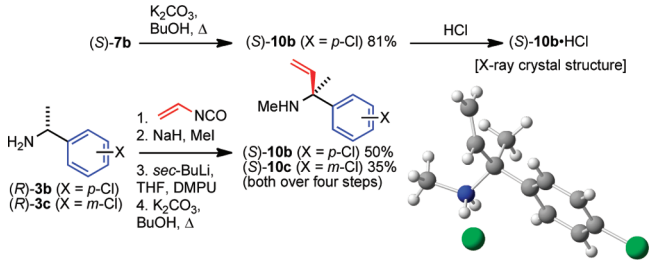
[a]Retention of stereochemistry proved for **7b** (see below); absolute configuration of other ureas **7** and of thiocarbamate **8** assumed by analogy.

(>99:1 e.r.) the product **7a** was obtained in enantiomerically pure form. The intermediate benzyllithium must therefore be configurationally stable[12] over the time scale of the migration, and the migration must occur with complete stereochemical fidelity.[13] Vinylation at the benzylic position α to nitrogen was likewise observed on lithiation of other *N*-vinylureas **4** and when enantiomerically pure starting materials were used, the products were also obtained enantiomerically pure.

N-Vinyl thiocarbamate **5** and carbamates **6** were lithiated under slightly modified conditions (with LDA) to minimize attack of the base on their carbonyl groups.[6] As with the ureas, lithiation took place at their benzylic center to give a dipole stabilized organolithium,[14] which in every case underwent vinyl migration to yield carbamoyl derivatives of the tertiary thiol **8** or tertiary alcohols **9a–c**. Thiocarbamate **8** formed with 80:20 e.r. under these conditions (and was essentially racemic if DMPU was used), and essentially racemic **9** was obtained under all conditions attempted.[12]

The products **7** of the rearrangements of ureas are allylic amines in protected form, and in many cases yields were compromised by their acid sensitivity. Conversion of the products to the α-tertiary allylic amine was achieved simply by treatment of the urea with K_2CO_3 in refluxing *n*-BuOH[5b] (Scheme 3). By combining into one operation the urea formation, rearrangement, and deprotection, it was possible to perform the direct stereospecific vinylation of the α-methylbenzylamines **3** in a single reaction vessel without purification of the acid-sensitive ureas. Treatment of **10b** with dry HCl yielded crystals of its hydrochloride salt, and single crystal X-ray analysis allowed us to establish its absolute configuration, thus confirming that the migration of the vinyl

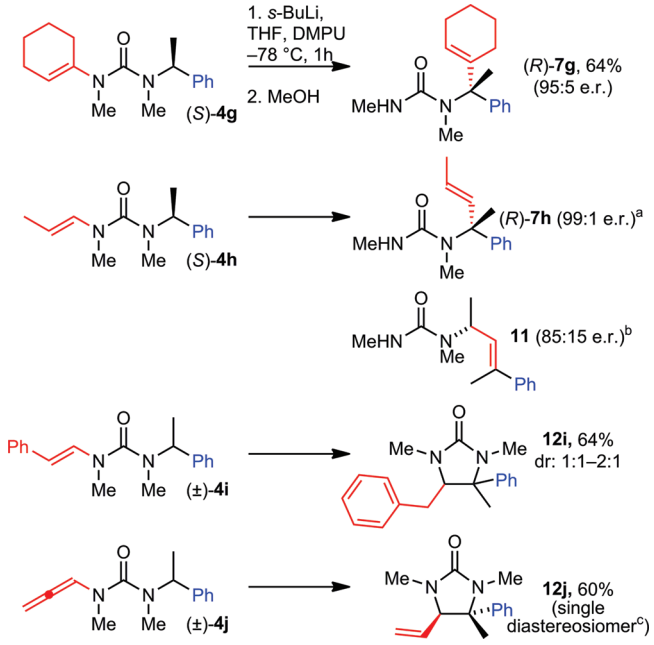
Scheme 3. Conversion to α-Tertiary Amines and X-ray Crystal Structure of (*S*)-10b•HCl



group to give **7b**, and hence presumably in other cases as well, is stereochemically retentive.[13]

Other *N*-alkenyl ureas **4g–j** were made from α-methylbenzylamine **3a** either by reaction with the alkenyl isocyanates (available by Curtius rearrangement of α,β-unsaturated carboxylic acids) or carbamoyl chlorides or by isomerization of an allylic or propargylic isomer (see SI for details). The alkenyl ureas were lithiated with *sec*-BuLi in THF and DMPU (Scheme 4). The cyclohexenyl group of (*S*)-**4g** rearranged

Scheme 4. Rearrangement and Cyclization of *N*-Alkenylureas[a]



[a]Too unstable to purify. [b]Isolated in 60% yield. Absolute stereochemistry not confirmed. [c]Relative stereochemistry deduced by NOE.

cleanly and streospecifically to give (*R*)-**7g** in good yield. Similarly, the propenyl group of (*S*)-**4h** rearranged to yield (*R*)-**7h** without loss of e.r., but on attempted purification **7h** rearranged with partial stereospecificity to the urea **11**. The styrenyl urea **4i** and the allenyl urea **4j** both returned imidazolidinones **12**, presumably because migration of the vinylic substituent in these cases is interrupted by the unusual stability of the benzylic or vinylic intermediate anion (see below for further mechanistic discussion). The benzyl-substituted product **12i** was obtained as a mixture of diastereoisomers, while the vinyl-substituted **12j** was isolated as a single diastereoisomer, probably as a consequence of equilibration

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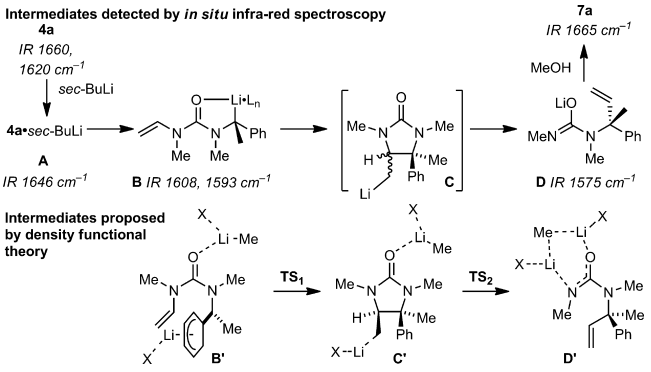
to the more stable epimer by deprotonation of the relatively acidic allylic position α to N.

The vinyl migration is effectively a nucleophilic substitution at a trigonal carbon atom, a reaction that is more commonly observed when anion stabilizing substituents allow an associative, addition−elimination mechanism to take place.[15] Further details of the migration of the vinyl group in urea **4a** and carbamate **6a** was provided by in situ IR spectroscopy (React-IR).[8,16] In order to avoid obscuring the carbonyl region of the spectrum, experiments were carried out in either THF or Et_2O in the absence of DMPU. In THF at −78 °C, the urea **4a** displays two absorptions at 1660 and 1620 cm^{-1} which disappear over a period of 30 s on treatment with *sec*-BuLi, being replaced (with no identifiable intermediates) by an absorption at 1575 cm^{-1} (Scheme 5). This peak can be

Scheme 5. Proposed Intermediates in the Rearrangement of 4a[a]



[a]X = DMPU or THF.

assigned to rearranged structure **D** since the same spectrum is generated by treating the rearranged product **7a** with BuLi. A similar reaction profile was observed for rearrangement of **6a** in THF.

Vinyl migration was much slower in Et_2O. Addition of *sec*-BuLi to **4a** in Et_2O in the absence or presence of LiCl gave a transient absorption at 1646 cm^{-1} which gave way over a period of seconds or minutes to a new intermediate with absorptions at 1608 and 1593 cm^{-1}. Quenching the reaction at this stage returned starting material, so we assume that the transient absorption arises from a prelithiated complex **A**[16] which is transformed into the intermediate lithiourea **B**. In the presence of LiCl, slowly warming the reaction to rt promoted rearrangement. At −25 °C the absorptions at 1608 and 1593 began to decrease in intensity, and at −15 °C, about 5 min later, a new absorption appeared at 1575 cm^{-1}, which we assign to structure **D** already identified. The formation of imidazolidinones from **4i** and **4j** points towards the intermediacy of a cyclic structure **C**, but we were unable to clearly identify absorptions corresponding to this proposed structure.

Density functional theory calculations[5a,8] (for computational details, see the SI) provided further illumination of the course of the vinyl migration. We considered a system composed of the lithiated derivative of **4a**, with an additional molecule of methyllithium coordinated to the urea carbonyl group and one molecule of either DMPU or THF coordinating each lithium atom, shown as structure **B′** in Scheme 5.[17] Starting from structure **B′**, nucleophilic attack of the benzylic anionic carbon atom on the vinyl group (TS_1) leads to the formation of a five-membered ring (**C′**). Interestingly, for computational models including either THF or DMPU, the lowest energy pathway from lithiated **4a** involves coordination of the lithium cation to the π-system of the phenyl substituent rather than to the benzylic carbon atom. In the transition state for C−C bond formation, this lithium cation migrates to the terminal carbon of the vinyl group in order to stabilize the developing negative charge, leading to stereochemically retentive formation of the new C−C bond, and with structure **C′** having a *syn* stereochemical relationship between the lithiomethyl group and the phenyl ring. Structure **C′** is predicted to be a shallow local minimum on the potential energy surface.

Breakage of the C−N bond adjacent to the lithiomethyl group (TS_2) completes the vinyl migration, leaving the negative charge delocalized over the urea group. In the product structure **D′** both lithium cations are bound to the urea anion as well as the methyl group, with one molecule of solvent coordinating each metal atom. The calculated potential energy profile and the optimized transition states are given in Figures 1 and 2, respectively, and show that the proposed mechanism is energetically feasible.

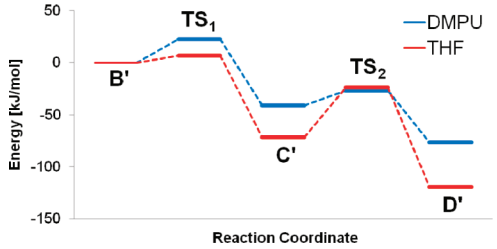


Figure 1. Calculated potential energy profile for the N→C vinyl migration at the B3LYP/6-311+G(2d,2p)//B3LYP/6-31G(d,p) level of theory.

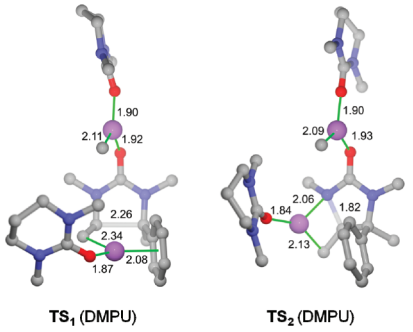


Figure 2. Optimized transition states at the B3LYP/6-31G(d,p) level of theory. Distances are in angstroms; hydrogen atoms have been omitted for clarity.

The overall barriers for the computational models containing THF and DMPU are 48.2 and 22.6 kJ/mol, respectively, in qualitative agreement with the observed differences in reactivity.

The cyclization of **4h** and **4i** arises because of the greater stability of the benzylic or vinylic organolithium intermediate corresponding to **C** and **C′** from these starting ureas. Nonetheless, successful migration of a styrenyl and a butadienyl group in **1a** and **1b** suggests that relatively small changes in structure can have a significant effect on the stability of any cyclic intermediate. It is possible that ring opening of **C** and its

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congeners is reversible,[18] and the successful migration of the styrenyl and butadienyl groups in Scheme 1 is made possible only by deprotonation of the final ring opened products, displacing the equilibrium.

The synthesis of quaternary centers bearing heteroatoms is in many cases challenging,[10] and the ability to deliver alkenyl substituents to such centers fills a useful gap in the synthetic repertoire.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental and characterization data, including ^{1}H and ^{13}C NMR spectra, for all new compounds. Computational and React IR data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

clayden@man.ac.uk

Notes

The authors declare no competing financial interest.

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(12) Dipole-stabilized benzylic organolithiums α to O or S are less configurationally stable than those α to N. See ref 1, pp 169−213.

(13) The X-ray crystal structure of (S)-**10b**•HCl has been deposited with the Cambridge Crystallographic Database, deposition number 861577. Related intramolecular arylations of ureas (ref 5a, 5e) and thiocarbamates (ref 6) proceed with retention of configuration, while arylations of carbamates (ref 5) proceed with inversion. In general, benzyllithiums react stereospecifically, but with the sense of retention or inversion being strongly dependent on conditions and the electrophile. For a discussion, see: References 1, pp 241−258, and 4. Also see: (a) Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297. (b) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344.

(14) α-O- and α-N-substituted organolithiums stabilized by carbamates and α-S-substituted organolithiums stabilized by thiocarbamates are well-established carbanion equivalents (ref 1). The equivalent ureas have risen to prominence only recently: (a) Clayden, J.; Dufour, J. *Tetrahedron Lett.* **2006**, *47*, 6945. (b) Clayden, J.; Turner, H.; Pickworth, M.; Adler, T. *Org. Lett.* **2005**, *7*, 3147. (c) Clayden, J.; Turner, H.; Helliwell, M.; Moir, E. *J. Org. Chem.* **2008**, *73*, 4415. For an overview, see: (d) Volz, N.; Clayden, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 12158.

(15) (a) For a recent discussion of nucleophilic aromatic substitution, see: Fernandez, I.; Frenking, G.; Uggerud, E. *J. Org. Chem.* **2010**, *75*, 2971. (b) For instances of substitution of vinylic leaving groups, see: Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley: NJ, 2007; pp 473−5. (c) Vinylic substitution may be achieved by 1,2-metallate rearrangement; see: Kocienski, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933.

(16) Full details of the in situ IR studies are provided in the Supporting Information. For recent studies of organolithium reactions using React-IR, see ref 3a and (a) Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Coldham, I.; Sanderson, A. *J. Am. Chem. Soc.* **2010**, *132*, 7260. (b) Pippel, D. J.; Weisenburger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919. (c) Rutherford, J. L.; Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **2002**, *124*, 264. (d) Sheikh, N. S.; Leonori, D.; Barker, G.; Firth, J. D.; Campos, K. R.; Meijer, A. J. H. M.; O'Brien, P.; Coldham, I. *J. Am. Chem. Soc.* **2012**, *134*, 5300. Several of these studies have noted transient species with reduced carbonyl stretching frequencies identified as 'pre-lithiation complexes' between the alkyllithium base and the substrate.

(17) Inclusion of a second molecule of alkyllithium in the computational model was found to be required to balance the negative charge building on the urea function upon opening of the cyclic intermediate.

(18) Evidence for the reversibility of the ring-opening step was also found when **7e** was treated with NaH, leading to ring closure to an imidazolidinone