Tandem β-Alkylation−α-Arylation of Amines by Carbolithiation and Rearrangement of N-Carbamoyl Enamines (Vinyl Ureas)

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The construction of tertiary alkylamines[1] is a synthetic challenge exacerbated by the poor electrophilicity of imines.[1e] Umpolung[2] approaches to the problem involving electrophilic attack on a nitrogen-stabilized carbanion[3] are a solution, and the use of nitroalkenes allows tandem addition of substituents β and α to a nitrogen function.[4] In this paper, we report our discovery that N-carbamoyl enamines (N-alkenyl ureas) likewise exhibit umpolung reactivity, undergoing addition of organolithiums to their otherwise nucleophilic β-carbons. The addition can be coupled with N → C aryl transfer within the lithiated urea intermediate,[5,6] allowing two new C−C bonds to the α and β carbons of the alkene to be formed in a single pot.

Alkenyl urea 1a was treated with t-BuLi in THF for 1 h at −78 °C. After the reaction was quenched with methanol, a single addition product 2a was obtained in 77% yield (Scheme 1); evidently, regioselective carbolithiation of 1 occurs readily under these conditions, presumably yielding initially a proposed benzylic organolithium 3 (R = t-Bu). Repeating the reaction with less hindered organolithiums revealed further unconventional reactivity. With n-butyllithium, the rearranged product 4a was obtained from 1 by N → C migration of the N-phenyl ring of 3.[5] The product 4a was straightforwardly converted to the tertiary alkyl amine 5a by heating in n-BuOH for 2.5 h,[7] indicating that this "alkylarylation" of enamine 1a could constitute a useful new method for the construction of multiply branched alkylamines.

Scheme 1. Umpolung Carbolithiation of Vinyl Ureas
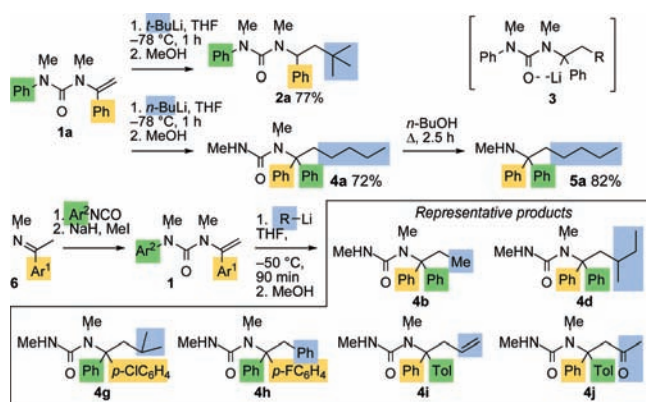
Other N-vinyl ureas 1b−g were made by N-carbamoylation of imines 6 and alkylation of the resulting ureas (Scheme 1). Table 1 shows the results of treating these N-vinyl ureas 1 with a range of organolithiums RLi in THF at −50 °C for 90 min.[8] In each case, carbolithiation followed by N-aryl migration resulted in tandem addition of two carbon substituents, R and Ar², across the electron-rich enamine double bond. Yields were good to excellent, and a range including methyl-, n- and sec-alkyl-, alkenyl-, and aryllithiums could be successfully added to the ureas.[9] Migration of a phenyl ring was generally faster and cleaner[8] than migrations of other (generally electron-rich) substituted aryl groups, and where a product could be

made in two ways by exchanging Ar¹ and Ar², the alternative with the more electron-rich Ar¹ group was preferable. Unsaturated products 4i and 4j containing alkene or carbonyl functions were available by addition of vinyllithium or ethoxyvinyllithium.

**Table 1.** Organolithium Additions to Vinyl Ureas 1

entry	s.m.	Ar¹	Ar²	R	4, yield (%)
1	1a	Ph	Ph	Bu	4a, 72[a]
2	1a	Ph	Ph	Me	4b, 78[b]
3	1a	Ph	Ph	i-Pr	4c, 74
4	1a	Ph	Ph	s-Bu	4d, 74
5	1a	Ph	Ph	Ph	4e, 77[c]
6	1b	Ph	p-MeOC₆H₄	i-Pr	4f, 75
7	1c	Ph	p-ClC₆H₄	i-Pr	4g, 72
8	1d	p-MeOC₆H₄	Ph	i-Pr	4f, 77
9	1e	p-ClC₆H₄	Ph	i-Pr	4g, 86
10	1f	p-FC₆H₄	Ph	Ph	4h, 78
11	1g	p-Tol	Ph	−CH₂=CH₂	4i, 75
12	1g	p-Tol	Ph	−CH(OEt)=CH₂	4j, 96[d]

[a] Deprotected to yield amine 5a (82%). [b] Deprotected to yield amine 5b (76%). [c] Deprotected to yield amine 5e (74%). [d] Mixture of 4j and a pyrimidinedione (see the Supporting Information).

Treating the propiophenimines 7 with aryl isocyanates gave vinyl ureas 8 with >96:4 E/Z selectivity (Scheme 2).[10] Methylation returned the alkenyl ureas 9 also as >96% E isomer. The Z isomers of 9 were available by a parallel route from allylamines 10,[11] which gave allylic ureas 11 upon treatment with aryl isocyanates. Methylation of 11 was accompanied by double-bond migration to give the ureas 9 with 98:2 Z/E selectivity.[12] (Z)-9 can alternatively be made directly from (E)-9 by formation of a (Z)-allyl anion represented as 12 (M = Li; X = Me): treatment of (E)-9a with LDA followed by methanol led to some decomposition but gave (Z)-9a with 98:2 Z/E selectivity.[13]

Scheme 2. Synthesis of (E)- and (Z)-Alkenyl Ureas
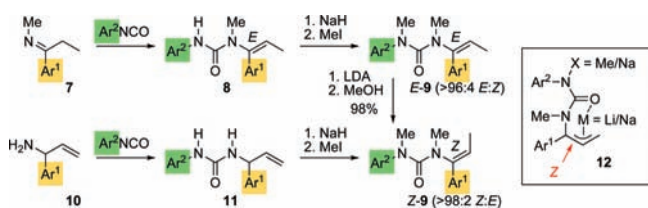

In THF at −40 °C, alkyllithiums RLi underwent clean addition to (E)-alkenyl ureas 9a−d (which have Ar² = Ph) and gave carbolithiation−rearrangement products 13a−e as single diastereoisomers (Table 2, entries 1−5). Ureas 13a−e were readily converted to single diastereoisomers of the amines 14 in refluxing n-butanol (Scheme 3).[7] The relative configuration of amine 14a was confirmed by an X-ray crystal structure[14] of its hydrochloride salt 14a·HCl (Scheme 3), which showed that 13 and hence 14 are formed by syn addition of R and Ar². As expected, transposition of Ar¹ and Ar² within the starting material led to an inversion of

Table 2. Organolithium Additions to Vinyl Ureas **9**

entry	s.m.	X in Ar¹ = C₆H₄X	Y in Ar² = C₆H₄Y	R	13 or 15, yield (%)	14, yield (%)
1	(E)-9a	p-Cl	H	i-Pr[a]	13a, 81	14a, 66
2	(E)-9a	p-Cl	H	n-Bu[a]	13b, 70	14b, 73
3	(E)-9b	p-F	H	i-Pr[a]	13c, 69	14c, 75
4	(E)-9c	p-Me	H	i-Pr[a]	13d, 60	14d, 70
5	(E)-9d	p-MeO	H	i-Pr[a]	13e, 76	14e, 70
6	(E)-9e	H	p-MeO	i-Pr[b]	epi-13e, 60	epi-14e, 70
7	(E)-9f	H	m-MeO	i-Pr[b]	13f, 60	14f, 69
8	(E)-9f	H	m-MeO	n-Bu[b]	13g, 65	−
9	(Z)-9a	p-Cl	H	i-Pr[b]	epi-13a, 75	epi-14a, 67
10	(Z)-9e	Ph	p-MeO	i-Pr[b]	13e, 54	14e, 70
11	(E)-9e	Ph	p-MeO	i-Pr[c]	15a, 85	
12	(E)-9e	Ph	p-MeO	n-Bu[d]	15b, 85	
13	(Z)-9e	Ph	p-MeO	i-Pr[b]	epi-15a, 44	
14	(E)-9f	Ph	m-MeO	i-Pr[c]	15c, 83	
15	(E)-9f	Ph	m-MeO	n-Bu[d]	15d, 85	
16	(E)-9f	Ph	m-MeO	t-Bu[a]	15e, 60	

[a] THF, −40 °C, 3−6 h. [b] (1) Tol, −40 °C, 1 h; (2) DMPU, −40 to +25 °C, 16 h. [c] Tol, −40 °C, 1−2 h. [d] Et₂O, −40 °C, 90 min.

Scheme 3. Stereospecific Reactions of (E)- and (Z)-Alkenyl Ureas
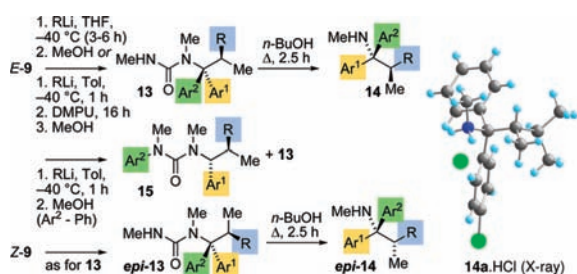
the relative configuration of the product (entries 5 and 6): the products from (E)-**9d** and (E)-**9e** are epimeric. The migrations of the more electron-rich rings of **9e** and **9f** were slower, and the best yields of **13f** and **13g** were obtained by carrying out the carbo-lithiation at −40 °C in toluene and adding DMPU to enforce rearrangement after the carbolithiation was complete (entries 6−8).[5a,15] Epimeric products were also formed when E starting materials were replaced with their Z isomers (entries 9 and 10). Thus, addition of i-PrLi to the Z isomer of **9e** yielded **13e**, which is epimeric with epi-**13e** derived from (E)-**9e** and identical to that produced from the "ring-transposed" (E)-**9d**.

Carbolithiation and rearrangement of **9** is slower than that of **1**. With **9e** and **9f**, the electron-rich aryl rings failed to migrate in the absence of DMPU,[15] and it was possible to isolate products **15** resulting from carbolithiation without rearrangement, even in THF (entries 11−16). Epimeric products were produced from (E)- and (Z)-**9f**.

Evidently, both the carbolithiation and aryl migration steps are stereospecific,[16] since either inverting the double-bond geometry in the starting material or exchanging the substituents Ar¹ and Ar² changes the configuration of the products. The crystal structure of **14a** indicates that the addition−migration process is mechanistically suprafacial. We propose that the reactions proceed by umpolung carbolithiation[17,18] of **9** (Scheme 4) to give a substituted benzyllithium **16** that is configurationally stable[19] on the time scale of the reaction. With electron-rich Ar², **16** may be trapped as **15** by retentive protonation.[17c,18a] In general, however, benzyllithium **16** undergoes retentive[5a,20] N → C aryl migration by attack of the organolithium center on the N-aryl ring Ar² (**17**), transferring Ar² to the position α to N and yielding lithiourea **18** and hence **13** upon protonation.

This new reaction allows the "1,2-alkylarylation" of a urea-substituted alkene and provides a valuable method for the construc-

Scheme 4. Proposed Mechanism
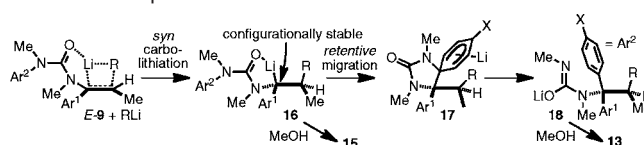
tion of heavily substituted amines from four components: a ketone, an amine, an isocyanate, and an organolithium.

Supporting Information Available: Full experimental procedures, characterization data for all compounds, and crystallographic data for **14a**·HCl (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) At −78 °C, yields were generally lower, and at least 2 h was required for completion, except in the case of a migrating Ph group, which proceeded within 2 h at −78 °C.
(9) Furyllithium and alkynyllithiums failed to add to **1**. Phenyllithium and vinyllithium, which added cleanly to **1**, failed to add to **9**.
(10) A review of enamides: Carbery, D. Org. Biomol. Chem. **2008**, 6, 3455.
(11) Allylamines **10** were made by Overman rearrangement of the cinnamyl alcohols (see the Supporting Information).
(12) We ascribe both the double-bond isomerization and the Z selectivity to deprotonation α to nitrogen by NaH to yield allyl anions represented as **12** (M = X = Na), which prefer a Z configuration. See: (a) Price, C. C.; Snyder, W. R. Tetrahedron Lett. **1962**, 3, 69. (b) Hutchby, M.; Lee, B. J. Org. Chem. **1989**, 54, 458. (c) Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. Chem. Rev. **1999**, 99, 665. Presumably, γ-deprotonation to give the same dianion from **8** is slower.
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(14) The X-ray crystallographic data has been deposited with the Cambridge Crystallographic Data Centre under deposition number 762201.
(15) The coordinating cosolvent DMPU typically accelerates nucleophilic attack of organolithiums on aromatic rings. See: Clayden, J.; Parris, S.; Cabedo, N.; Payne, A. H. Angew. Chem., Int. Ed. **2008**, 47, 5060, and references therein.
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