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Studies on the asymmetric cycloaddition of 2-azaallyl anions with alkenes

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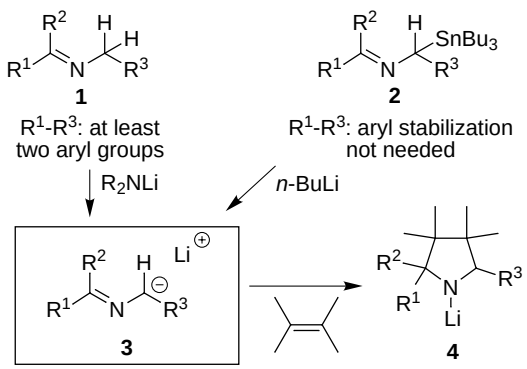
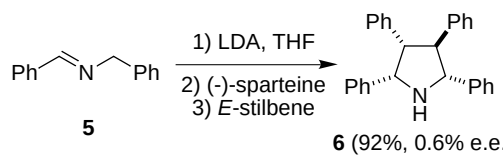
Abstract—A preliminary survey of strategies for the asymmetric cycloaddition of nonstabilized 2-azaallyllithiums with alkenes is reported. The chiral diamine (–)-sparteine exerted little, if any, absolute stereocontrol. The attachment of a chiral auxiliary to the anion was more successful, leading to the first example of an asymmetric cycloaddition of a 2-azaallyllithium (**24** to **25**, 98% e.e.).

The anionic cycloaddition of 2-azaallyl anions with alkenes has been known since the early 1970s, beginning with the initial work by Kauffmann on 1,3-diphenyl-2-azaallyllithium[1] and continuing to our own work on less-stabilized alkyl-substituted 2-azaallyllithiums derived from tin–lithium exchange[2] (Scheme 1). To the best of our knowledge, no examples of asymmetric versions of these cycloadditions have been reported.[3] Herein we report our initial survey of strategies for asymmetric 2-azaallyl anion cycloadditions, culminating in the first example of a highly enantioselective example of this process.



Scheme 1.

The most convenient strategy for the asymmetric cycloaddition of 2-azaallyllithiums with alkenes would be to use a chiral additive that would ligate the lithium ion. In the Kauffmann process, wherein a base is used to deprotonate an imine (e.g. **5**), a chiral solvating agent could be used, or perhaps a chiral lithium dialkylamide would serve as both a base and a chiral lithium-solvating agent. The disadvantages of this approach are several-fold. First, it is difficult to rationally design a ligand/azaallyllithium system due to the uncertainties surrounding the structure of such complexes. Second, the stereochemical information embodied in the lithium-ligating agent may be too remote from the site of cycloaddition for high enantioselectivity. Third, even if a particular system could be optimized, it may not be relevant to a broader group of anions. Finally, the Kauffmann-type anions are limited in scope, producing polyarylpyrrolidines such as **6**. Nonetheless, we examined this approach briefly. Our initial attempts at using a chiral lithium-solvating agent in the Kauffman strategy were unsuccessful, e.g. Eq. (1). While the cycloaddition was very efficient in the presence of the chiral diamine (–)-sparteine,[4] the cycloadduct **6** was produced in low e.e.[5]



(1)

Similarly, the presence of (–)-sparteine during cycloadditions of less-stabilized 2-azaallyllithiums was also ineffective (Scheme 2), producing the racemic pyrroline

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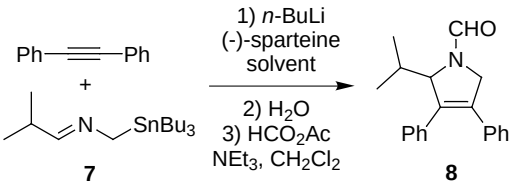
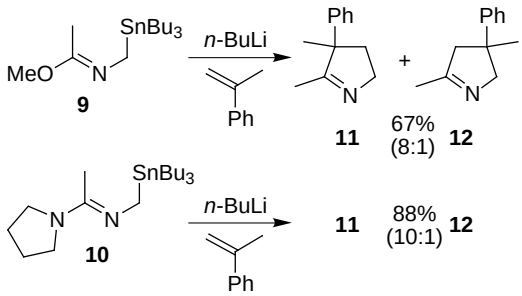
Table 1.



Solvent	Additive	Yield (%)	% e.e.
THF	None	49	0
THF	(−)-Sparteine	17	0
Toluene	(−)-Sparteine	39	6

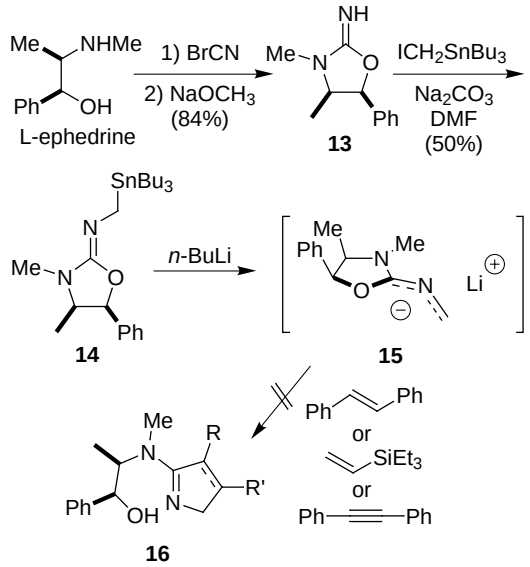
8 from **7** in lower yield than in the absence of the ligand. Running the cycloaddition in toluene with sparteine restored the efficiency of the cycloaddition and produced non-racemic material, although in only 6% e.e. (Table 1).[6]

Due to the limitations of the chiral ligand approach outlined above, we sought to examine the placement of a chiral auxiliary on the 2-azaallyllithium. We chose to use a heteroatom-linked auxiliary, since we had previously shown that heteroatom-substituted 2-azaallyllithiums could be generated from tin-bearing imidates (e.g. **9**), amidines (e.g. **10**), and thioimidates, producing 1-pyrrolines such as **11** and **12** after ejection of the heteroatom group after the cycloaddition (Scheme 2).[7,8]



Scheme 2.

Our first attempt at using a heteroatom-linked chiral auxiliary focused on the 2-iminooxazolidine **14**, which by virtue of its two points of attachment should produce a relatively rigid and facially biased 2-azaallyllithium intermediate **15**. Attaching the auxiliary via two heteroatoms would have an additional benefit in that it remains attached after the cycloaddition, allowing the separation of any diastereomers that may result, as well as producing a material at the oxidation state of a lactam, i.e. the amidine **16**. Transformation of L-ephedrine into the known[9] 2-iminooxazolidine **13**, followed by *N*-alkylation afforded **14**. Unfortunately, transmetalation of **14** in the presence of *trans*-stilbene, triethylvinylsilane or diphenylacetylene did not afford any identifiable products (Scheme 3).



Scheme 3.

The failure of the cycloaddition of **15** may be due to unfavorable electron-pair repulsion between the 4π-electron system of the 2-azaallyllithium and the lone pairs present on the nitrogen and oxygen of the oxazolidine ring, as shown by structure **15** of Fig. 1. We thus redesigned our chiral auxiliary based on several points. First, from the *allyl* anion literature, it is known that a heteroatom at the terminus of an anion prefers to orient its lone pair perpendicular to the allyl anion π-system, thus minimizing repulsive interactions between filled orbitals.[10] Second, structural studies on a number of allyl anions show the metal to be π-complexed.[11] Particularly relevant are solution[12] and solid-state structural[13] studies on 1,3-diphenyl-2-azaallylsodium, which clearly show the metal to be π-complexed. The first design element we considered was to excise the ring in **15** that enforces unfavorable

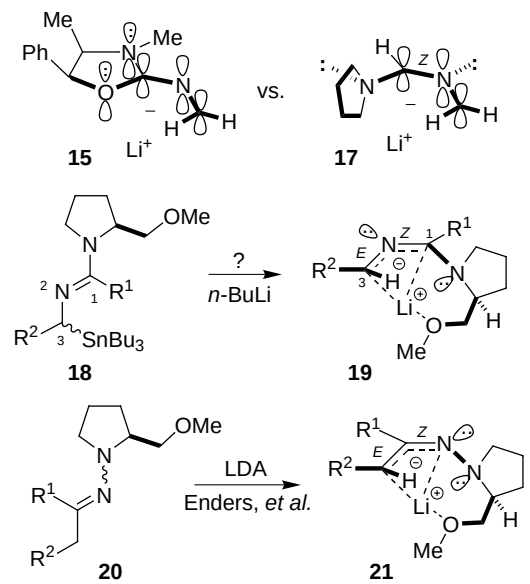
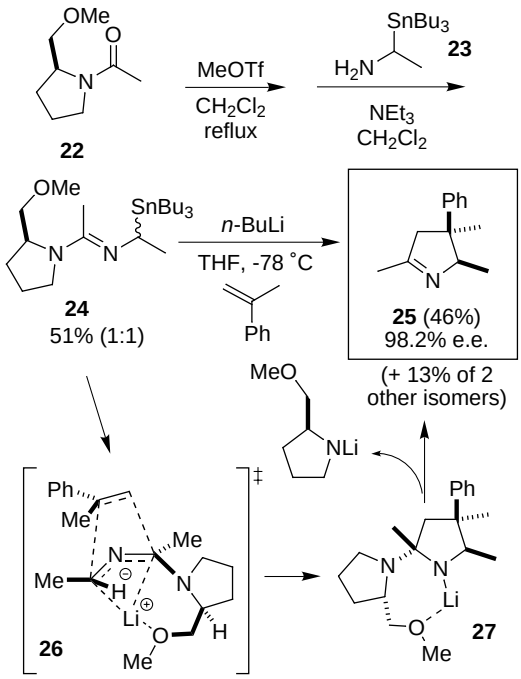


Figure 1.

electronic interactions, but retain a heteroatom (or perhaps two) at one terminus of the 2-azaallyllithium system. For example, a more flexible anion such as 1-pyrrolidino-2-azaallyllithium **17** allows bond rotation such that the nitrogen lone pair can be orthogonal to the 2-azaallyllithium π-system, as shown in Fig. 1. Simple MNDO calculations support this structure. Note that the *Z* geometry of **17** is shown, in accord with the literature of 1-amino allyl anions[10] and 1-amino-1-azaallyl anions (i.e. α-lithiated hydrazones),[14] where a strong preference for such a geometry is found. The success of the cyclizations of **9** and **10** (Scheme 2) further supports the idea that such conformationally flexible heteroatom-substituted anions are viable. The second design element that was applied was to introduce a chiral center on the pyrrolidine ring of **17** that bears a lithium-chelating substituent in order to provide internal chelation of the π-complexed lithium ion, directing it to one of the two diastereotopic faces of the anion. Based on these ideas, an *O*-methyl prolinol-derived auxiliary was deemed attractive, generalized by **19**, available from transmetalation of the stannyl amidine **18**.[15] This strategy is similar to that employed by Enders and co-workers in their work on chiral lithiated hydrazones. For example, deprotonation of the SAMP-hydrazone **20** is thought to produce the 1-azaallyl anion **21**, which differs from **19** by a reversal of the CN linkage.[14a,d,i] Two significant issues will remain unresolved until experimental results are obtained. First, does the geometry of **18** correlate with the geometry of **19**? While the *E* isomer of the amidine **18** is preferred, the 1*Z*,2*E* isomer of **19** should be preferred. Will the barrier to bond rotation be low enough to allow **19** to form, or will the geometry of **18** be conserved, producing the 1*E*,2*E* isomer of **19**? A similar issue arises in Enders' chemistry; the geometry of **21** is independent of the geometry of **20**, indicating that bond geometrical interconversion is possible. Second, which face of the anion **19** will combine with the anionophile? The top face (as drawn) appears least sterically hindered, and would thus result in inversion of stereochemistry with respect to the lithium atom. On the other hand, organolithiums often prefer to react with electrophiles with retention of configuration. Further confusing the issue is the mechanism of the cycloaddition itself. A stepwise cycloaddition (via carbolithiation of the anionophile followed by a 5-*endo*-*trig* cyclization) is a viable alternative to a concerted cycloaddition.[16–18] Thus, for example, a concerted cycloaddition might proceed from the least hindered face of the anion, while a stepwise cycloaddition involving carbolithiation as the first step might involve a retentive pathway proceeding from the same face as the lithium ion. For the analogous 1-azaallyl anions **21**, Collum favors approach of the electrophile from the side of the anion opposite to the lithium,[14f] while Enders and Boche favor a 'metallo-retentive S_E2'-front' mechanism.[14h]

To study this approach, the amidine **24** was synthesized as shown in Scheme 4. *O*-Methylation of the acetamide **22** (derived from L-proline) followed by combination of the resultant iminium salt[19,20] with racemic **23**[21] gave **24**



Scheme 4.

in moderate yield as a 1:1 mixture of diastereomers. Transmetalation in the presence of α-methylstyrene gave the pyrroline **25**, presumably via **26** and **27**. A small amount of a mixture of two other isomers was also isolated, but their structures were not determined. The major product **25** was found to have an e.e. of greater than 98%, as determined by HPLC using an amylose carbamate stationary phase.[22] The absolute configuration of **25** has not yet been determined, and is proposed based on our rationale for the structure of the anion **19** combined with a concerted cycloaddition via an invertive pathway (see above).

In conclusion, a survey of various strategies for accomplishing an asymmetric cycloaddition of a 2-azaallyl anion with an alkene has resulted in the first successful example of such a process. Details of the scope[23] and absolute stereoselectivity of this process will follow in a full report.

Experimental

(2*S*,3′*RS*)-1-(2-Aza-1-methyl-3-(tri-*n*-butylstannyl)-1-butenyl)-2-(methoxymethyl)pyrrolidine (24): Methyl triflate (90 μL, 0.80 mmol) was added to a solution of the known[24] amide **22** (120 mg, 0.78 mmol) in CH_2Cl_2 (10 mL). After heating at reflux for 24 h, the mixture was allowed to cool to room temperature. In a separate flask, *N*-[1-(tri-*n*-butylstannyl)ethyl]phthalimide (360 mg, 0.78 mmol)[8] and hydrazine monohydrate (3.0 mL, 62 mmol) were dissolved in EtOH (25 mL) and heated at reflux. After 6 h, the mixture was concentrated to provide a white mass, which was diluted with ether and washed five times with water. The organic phase was dried (Na_2SO_4), filtered, and concentrated to provide the crude amine **23** as an oil.[8] This material was dis-

solved in dichloromethane (3 mL), mixed with triethylamine (0.20 mL, 1.4 mmol), and added to the triflate salt prepared above. After 12 h, the mixture was diluted with ether and washed with 10% aqueous NaOH, and the organic phase was dried (Na_2SO_4), filtered, and concentrated. Chromatography (hexane to EtOAc to 15% MeOH/EtOAc gradient on alumina) afforded 190 mg (51%) of the title compound as an inseparable 1:1 mixture of diastereomers, $R_f=0.20$ (15% MeOH/EtOAc on alumina). Partial data for one diastereomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.34 (s, 3H). Partial data for the other diastereomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.32 (s, 3H). Data for mixture: IR (neat) 1605 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.10–4.00 (br s, 1H), 3.64–3.55 (m, 1H), 3.46–3.40 (m, 1H), 3.40–3.28 (m, 4H), 3.28–3.05 (m, 2H), 1.88–1.72 (m, 7H), 1.50–1.40 (m, 6H), 1.40–1.23 (m, 6H), 0.95–0.69 (m, 15H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 151.4, 150.4, 74.1, 74.0, 58.9, 58.9, 56.1, 56.0, 47.9, 45.8, 29.3, 28.3, 28.1, 27.8, 27.6, 27.3, 27.1, 23.5, 23.4, 23.0, 22.8, 15.6, 13.8, 13.7, 8.9; MS (CI, NH_3) m/z (rel. int.) 475 (9, M+H), 474 (7, M$^+$), 185 (38), 184 (97), 183 (100); HRMS (CI, NH_3) calcd for $C_{22}H_{47}N_2O^{120}Sn$ (M+H)$^+$ 475.2710, found 475.2709.

(2*R*,3*S* or 2*S*,3*R*)-2,3,5-Trimethyl-3-phenyl-3,4-dihydro-2*H*-pyrrole (25): A solution of the amidine **24** (435 mg, 0.92 mmol) and α-methylstyrene (240 mg, 2.0 mmol) in THF (2 mL) was added in a dropwise fashion to a solution of *n*-butyllithium (1.7 mL, 4.6 mmol, 2.7 M in hexanes) in THF (2 mL) at −78°C. After 2 h, excess methanol was added and the mixture was diluted with ether and washed with water. The organic phase was dried (Na_2SO_4) and concentrated. Chromatography (0–100% EtOAc/hexane gradient) first afforded 21 mg (13%) of a mixture of two pyrrolines of undetermined structure, $R_f=0.15$ (EtOAc), presumed to be diastereomeric and/or regioisomeric with the pyrroline **22**. Partial data for the first minor isomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.92 (s, 3H), 1.53 (s, 3H), 1.37 (d, 3H, $J=6.9$ Hz). Partial data for the second minor isomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.80 (s, 3H), 1.62 (s, 3H), 1.42 (d, 3H, $J=6.9$ Hz). Further elution gave 80 mg (46%) of the title compound, the relative configuration of which was determined by difference NOE spectroscopy. Separation of the enantiomers of **22** by chiral HPLC revealed an enantiomeric excess of 98.2%. Data for **22**: $R_f=0.10$ (EtOAc); IR (neat) 1646 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.34–7.21 (m, 5H), 4.08 (q, 1H, $J=7.0$ Hz), 3.12 (d, 1H, $J=16.6$ Hz), 2.58 (d, 1H, $J=16.7$ Hz), 2.10 (s, 3H), 1.39 (s, 3H), 0.72 (d, 3H, $J=6.9$ Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 173.0, 145.6, 128.0, 126.7, 125.9, 49.8, 29.7, 20.5, 17.3; MS (EI, 70 eV) m/z (rel int) 188 (6, M+1), 187 (28, M$^+$) 172 (11), 69 (100); HRMS (EI, 70 eV) calcd for $C_{13}H_{17}N$ M$^+$ 187.1361, found 187.1347.

Acknowledgements

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22. The enantiomeric excess of **25** was determined by HPLC using a Chiral Technologies CHIRALPAK AD column, 0–3% *i*PrOH/hexane gradient, 0.5 mL/min flow rate. A sample of racemic **25** was prepared from *N*,*N*-dimethyl-*N*′-[1-(tributylstannyl)ethyl]acetimidamide [$Me_2NC(CH_3)$-$NCH(SnBu_3)Me$], α-methylstyrene, and *n*-BuLi. The two enantiomers of racemic **25** eluted at 55.1 and 55.2 min using this separation technique. Examination of **25** derived from **24** by HPLC revealed the two enantiomers at 55.2 and 56.9 min with relative areas of 99.2:1.00, corresponding to an enantiomeric excess of 98.2%.
23. In preliminary results, a cycloaddition of the anion derived from **24** with triethylvinylsilane was also successful, affording a 49% yield of *trans*-2,5-dimethyl-4-triethylsilyl-4,5-dihydro-3*H*-pyrrole. The e.e. of this cycloadduct has not yet been determined.
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