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Regio- and enantioselective copper-catalyzed addition of dialkylzinc reagents to cyclic 2-alkenyl aziridines

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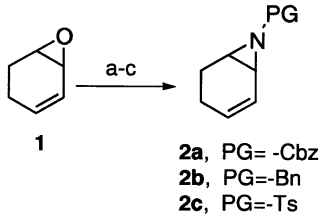
Abstract—The reactions of some organocopper reagents with cyclic 2-alkenyl aziridines were examined. The stereoselectivity of the addition reaction of dialkylzinc can be strongly influenced by the use of phosphoramidites as ligands for copper. Chiral copper complexes of 2,2′-binaphthyl-based phosphoramidites were shown to be highly effective catalysts for the regio- (S_N2') and *anti*-stereoselective addition of dialkylzinc reagents to these compounds according to a kinetic resolution protocol. The corresponding new cyclic allylic amine reaction products were obtained with a good enantioselectivity (83% ee).

Activated aziridines, notably 2-alkenyl aziridines, are versatile synthetic intermediates for the synthesis of biologically important compounds.[1] In the past few years great advances have been reported in the development of synthetic methods for the nucleophilic ring-opening of 2-alkenyl aziridines.[2] In particular, the use of organocuprates as the nucleophiles has emerged as a powerful and stereoselective synthetic method for the preparation of aliphatic (*E*)-allylic amines.[3] These synthetically useful compounds can be obtained in an enantiomerically pure form by means of a chiral pool approach starting from non-racemic aminoacids.[4] However, to the best of our knowledge, there are no reports about the catalytic and enantioselective addition of organometallic reagents to these carbon electrophiles. Based on the copper-phosphoramidite catalyzed addition of dialkylzinc reagents to racemic 2-alkenyl oxiranes recently developed by us,[5] we envisaged that highly reactive 2-alkenyl aziridines might be suitable candidates in our reaction protocol. In this communication we wish to report our preliminary results for this reactivity and the stereoselective synthesis of previously unobtained cyclic primary allylic amines.

The synthesis of vinyl aziridines of type **2** was accomplished by azidolysis of 1,3-cyclohexadiene monoepoxide **1** with NaN_3 mediated by 0.75 M $LiClO_4$ in anhydrous CH_3CN (85% yield for step a) (Scheme 1).[6] Subsequent ring closure of the crude mixture containing the azido alcohols with PPh_3 in CH_3CN[7] afforded a crude 2-alkenyl-NH aziridine which was not isolated but directly derivatized with CBzCl/Py/DMAP or $BnBr/K_2CO_3$ to give after chromatographic purification (SiO_2 eluting with hexanes/AcOEt/NEt_3 = 85:10:5) the pure protected aziridines **2a** (45% for steps b and c) and **2b** (42%), respectively (Scheme 1). In our hands it was not possible to obtain the N-Ts aziridine **2c** in a pure state, probably due to the ring-opening of this compound during chromatographic purification. Moreover, it is worthy of mention that all the attempted alternative syntheses of vinylaziridines of type **2** by direct diene aziridination with PhI=NTs[8] or via N-substituted 1,4-aminoalcohols using Mitsunobu conditions,[9] were unsuccessful.



Scheme 1. *Reagents and conditions*: (a) $LiClO_4/CH_3CN/NaN_3$ (85%); (b) PPh_3/CH_3CN rt 1h than reflux 12 h; (c) BnOCOCl/NEt_3/Et_2O for **2a** (45%); $BnBr/K_2CO_3/CH_3CN$ for **2b** (42%); TsCl/Py/DMAP (cat) for **2c** (see text).

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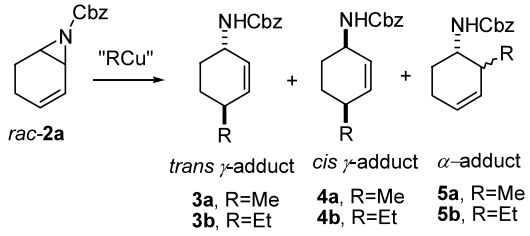
Table 1. Addition of R_2Zn to vinyl aziridines **2a** and **2b**[a]

Entry	Substrate	L*	R_2Zn (equiv.)	Time (h)	Conv. (%)[b]	*trans*/*cis*[c]	Ee (%)[d]
1	**2a**	None	Et_2Zn (1.50)	3	>95	48/52	
2	**2a**	(±)-**L1**	Et_2Zn (1.50)	4	100	95/5	
3	**2b**	**L1**	Et_2Zn (1.50)	18	<5	N.d.	N.d.
4	**2a**	**L1**	Et_2Zn (0.75)	2	55	93/7	61
5	**2a**	**L2**	Et_2Zn (0.55)	2	42	91/9[e]	78
6	**2a**	**L1**	Et_2Zn (0.55)	2	50	>98/<2[e]	4
7	**2a**	**L3**	Et_2Zn (0.50)	2	45	95/5[e]	52
8	**2a**	**L2**	Et_2Zn (1.50)	18	100	80/20	8
9	**2a**	**L4**	Me_2Zn (1.50)	18	>95	>95/<5[e,f]	5
10	**2a**	**L1**	Me_2Zn (3.00)	4	>95	>95/<5[e,f]	8
11	**2a**	**L2**	Me_2Zn (0.40)	2	48	>95/<5[e]	83

[a] All reactions were performed in accordance with the typical procedure (see Ref. 19), [$Cu(OTf)_2$ = 3 mol%, L* = 6 mol%, −78°C for kinetic resolution (entries 4, 5, 6, 7, 11); from −78°C to 0°C for the remaining entries]. The reaction reported in entry 6 was performed in THF.
[b] Conversion determined by ^1H NMR analysis of the crude mixture.
[c] Determined by HPLC analysis on Daicel Chiralcel OD-H.
[d] Determined by HPLC analysis on Daicel Chiralcel OD-H. The enantiomeric excess refers to the *trans* compounds **3a**,**b**.
[e] Calculated after chromatographic purification.
[f] A substantial amount (15–20%) of α-adduct **5a** was obtained. (N.d. = not determined).



Scheme 2. Addition of organocopper reagents ('RCu') to (±)-**2a**.

The reaction of Cbz-protected aziridine **2a** with Me_2CuLi in anhydrous Et_2O was not S_N2'-regioselective as found for aliphatic *N*-diphenylphosphinyl vinyl aziridines[10] seeing that it afforded a relatively complex mixture in which compound **5a** (α-adduct) represented the major alkylation product (Scheme 2).[11] When the CuCN (20 mol%) catalyzed addition of EtMgBr to **2a** was employed,[12] a complex mixture of products was obtained. Interestingly, the addition of Et_2Zn (1.5 equiv.) in the presence of $Cu(OTf)_2$ (0.03 equiv.) occurred smoothly,[13] (>95% conversion in 3 h, at −78°C up to −10°C) and afforded an equimolar mixture of the *cis*,*trans*-allylic amines **3b** and **4b**, (γ-adducts) (entry 1, Table 1).[14] The obtainment of substantial amounts of *syn*-addition products is in sharp contrast with the related epoxide **1**, where a uniformly high *anti*-stereoselectivity was found with organocopper reagents.[15] Usually a copper catalyzed allylic alkylation occurs in an *anti* fashion but a *syn*-stereoselective process had already been found in copper allylic substitution reactions with a reagent-coordinating leaving group.[16] It is therefore likely also in the present case that a complexation of the copper with the nitrogen atom of the vinyl aziridine may occur (see A in Figure 1). In this picture, the pseudo-axial addition of the organometallic reagents probably gives rise to an σ-allyl copper(III) (**B**) and the subsequent reductive elimination may afford the *cis*-adduct of type **4**.

The *syn*-stereoselective pathway can be drastically suppressed through the use of an external (chiral) ligand for copper. For example the use of catalytic amounts of chiral copper complexes with racemic (*R*,*S*,*S*)(*S*,*R*,*R*)-(**L1**)[17] (Fig. 2) as a catalyst for the addition of Et_2Zn (1.5 equiv.) to **2a** made it possible to obtain a 95:5 *anti*/*syn* stereoselectivity (entry 2, Table 1). The nature of the protecting group on alkenyl aziridines exerted a great influence on their reactivity.[18] Whereas the Cbz protecting group proved to be optimal with respect to

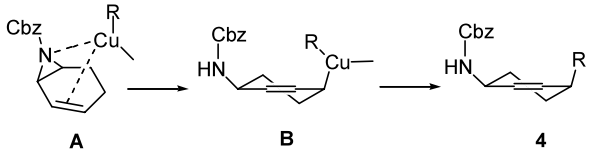


Figure 1. Interpretation of the *syn*-stereoselective S_N2'-process.

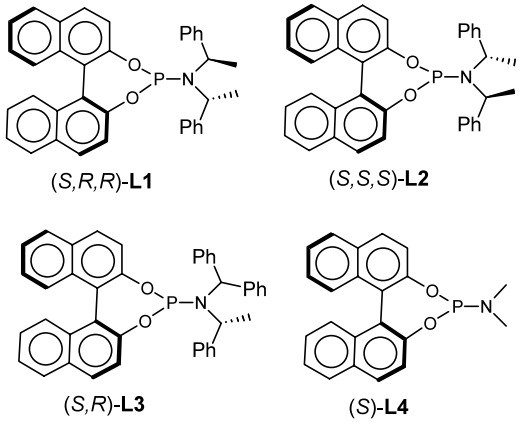
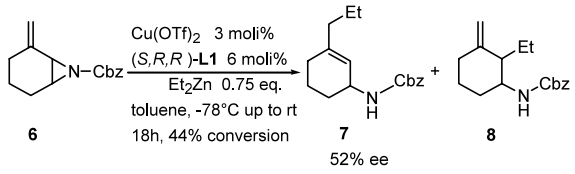


Figure 2. Phosphoramidites used as ligands for copper.



Scheme 3. Addition of Et_2Zn to exo-methylidene aziridine **6**.

stability and reactivity, the benzyl-protected aziridine **2b** showed to be not enough reactive in our reaction conditions. With this substrate, only trace amounts of addition products were obtained, even using an excess of Et_2Zn and a prolonged reaction time and therefore it was not further examined (entry 3). The use of 0.75 equiv. of Et_2Zn in a short reaction time (2 h), following a kinetic resolution protocol, afforded the corresponding allylic amine **3b** with a high diastereoselectivity and a moderate enantioselectivity (61% ee) (entry 4).[19]

A higher enantioselectivity (78% ee), albeit associated with a lower value of conversion, was obtained by the use of chiral ligand **L2** (entry 5). When a similar reaction was carried out in THF it proved to be comparably fast and diastereoselective but delivered **3b** with poor enantioselectivity (entry 6). The use of chiral ligand **L3**,[20] possessing a non *C*-2 symmetric amine moiety, afforded **3b** with an excellent diastereoselectivity and a moderate enantioselectivity (entry 7). Very interestingly with a 2-alkenyl aziridine substrate, such as **2a**, the regiodivergent kinetic resolution (*RKR*) encountered when related 2-alkenyl oxiranes systems were used in the same reaction conditions is not operative.[21] In fact, when a reaction was performed in the presence of a chiral copper complex with **L2** with an excess of Et_2Zn the γ-adduct was obtained (8% ee) together with only trace amounts of α-adduct **5b** (<5%). The only visible effect was the increase in the *syn*-adduct **4b** (entry 8). The absence of an effective in situ regiodivergent chiral recognition between the catalyst and the enantiomers of substrate **1a** was confirmed by the use of an excess of Me_2Zn. In this case the reaction gave also a substantial amount (20% of the crude mixture) of α-adduct **5a** when the reaction is carried out up to completion, but both α- and γ-adducts were obtained essentially as racemates (entries 9 and 10). The use of 0.4 equiv. of Me_2Zn afforded compound **3a** with the best enantioselectivity found for this reaction (83% ee at 48% conversion, entry 11). Although the enantioselectivity levels obtained for this reaction are not always exceedingly high, the fact that compounds **3a**,**b** are solid provides a way to further enhance their enantiopurity.

The new 2-alkenyl aziridine **6**, bearing an *exo*-methylidene unit in the allylic position with respect to the aziridine ring, was obtained from the corresponding vinyl epoxide via azidolysis and subsequent ring-closure. This compound proved to be less reactive in our reaction conditions (see Scheme 3). However, it was possible to obtain the corresponding γ-addition product **7** with a 52% ee together with a minor amount (14%) of the α-adduct 8.[22]

In summary, the present work represents the first report demonstrating a successful combination of an organometallic reagent and an external chiral ligand in a kinetic resolution protocol for the nucleophilic displacement of racemic cyclic 2-alkenyl aziridines. Whereas the use of organocopper reagents revealed also a *syn*-stereoselective pathway for this reaction, copper complexes with phosphoramidites were found to give an enhanced *anti*-stereoselectivity in the addition of organozinc reagents. The corresponding new cyclic primary allylic amine reaction products, which are versatile and valuable building blocks, were obtained with a good regio- and enantioselectivity.

Acknowledgements

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11. Determined by ^1H NMR of the crude mixture. Compound **5a** (obtained in mixture with an unidentified com-

pound after chromatography): $R_f = 0.29$ (hexanes:AcOEt, 8:2). ^{1}H NMR ($CDCl_3$) δ 4.90–5.19 (m, 2H), 5.08 (s, 2H), 4.58–4.72 (m, 1H), 3.45–3.64 (m, 1H), 1.05 (d, 3H, $J = 7.2$ Hz).

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18. Spectral data for 2-alkenyl-aziridines. Compound **2a**: ^{1}H NMR ($CDCl_3$) δ 7.40–7.33 (m, 5H), 6.05–5.97 (m, 1H), 5.92–5.85 (m, 1H), 5.13 (s, 2H), 3.10–3.00 (m, 1H), 2.90–2.84 (m, 1H), 2.29–2.20 (m, 1H), 2.08–1.98 (m, 2H), 1.59–1.44 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.2, 135.9, 131.7, 128.5, 128.2, 122.4, 69.7, 68.1, 63.8, 56.9, 39.8, 33.8, 20.6, 19.4. Compound **2b**: ^{1}H NMR (C_6D_6) δ 7.42–7.02 (m, 5H), 6.06–5.98 (m, 1H), 5.73–5.61 (m, 1H), 3.28 (ABq, 2H, $J = 13.7$ Hz), 2.46–2.19 (m, 1H), 2.02–1.16 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 140.2, 130.11, 128.12, 127.3, 125.4, 63.8, 42.7, 36.05, 23.11, 20.52. Compound **6**: ^{1}H NMR (C_6D_6) δ 7.27–7.07 (m, 5H), 5.12 (d, 1H, $J = 1.0$ Hz), 5.05 (s, 2H), 4.92 (d, 1H, $J = 1.0$ Hz), 2.93 (d, 1H, $J = 6.1$ Hz), 2.64–2.59 (m, 1H), 2.18–2.04 (m, 1H), 1.81–1.74 (m, 2H), 1.50–1.20 (m, 2H), 1.16–0.95 (m, 1H). ^{13}C NMR (C_6D_6) δ 163.6, 142.8, 137.3, 129.1, 128.9, 128.5, 127.9, 114.8, 68.4, 42.1, 39.2, 29.8 23.9, 20.9.
19. **Typical procedure: preparation of 3b** (entry 4): A solution of $Cu(OTf)_2$ (5.4 mg, 0.015 mmol) and chiral ligand (*S*,*R*,*R*)-**L1** (16.2 mg, 0.03 mmmol) in anhydrous toluene (1.5 mL) was stirred at rt for 40 min. The colorless solution was cooled to −78°C followed by subsequent addition of a solution of **1a** (229 mg, 1.0 mmol) in toluene (0.5 mL). After 5 min, Et_2Zn (0.68 mL of a 1.1 M solution in toluene, 0.75 mmol) was added. After 2 h at −78°C (55% conversion) the mixture was quenched with saturated aqueous NH_4Cl solution (5 mL). Extraction with Et_2O (2×35 mL) and evaporation of the dried ($MgSO_4$) organic phase afforded a clean crude mixture (250 mg). Compound **3b** was obtained in a pure state (90 mg, 63% isolated yield, based on reacted aziridine) as a solid after flash chromatography (SiO_2) eluting with hexanes/AcOEt (9:1+1% NEt_3). Mp: 71–73°C (not recrystallized). $R_f = 0.32$ (hexanes:AcOEt, 8:2). $[\alpha]_D^{20} = -70.5$ (*c* 0.91, MeOH). ^{1}H NMR ($CDCl_3$) δ 7.40–7.20 (m, 5H), 5.68 (d, 1H, $J = 10.6$ Hz), 5.53 (d, 1H, $J = 10.6$ Hz) 5.10 (s, 2H), 4.80–4.55 (m, 1H), 4.30–4.08 (m, 1H), 2.10–1.10 (m, 7H), 0.95–0.80 (t, 3H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 156.4; 137.2; 135.4; 129.0; 128.6; 128.5; 67.1; 48.3; 37.3; 30.2; 29.1; 27.5; 11.0. The enantiomeric excess (61%) was determined by HPLC on a Daicel Chiralcel OD-H (hexanes/IPA = 95:5). Retention times were: 18 min (major), 25 min (minor). Compound **3a**: a solid. Mp: 80–83°C (not recrystallized). $R_f = 0.27$ (hexanes:AcOEt, 9:1). ^{1}H NMR ($CDCl_3$) δ 7.38–7.31 (m, 5H), 5.63 (d, 1H, $J = 10.3$ Hz), 5.51 (d, 1H, $J = 10.3$ Hz), 5.09 (s, 2H), 4.15–4.30 (m, 1H), 4.62–4.70 (m, 1H), 2.01–2.25 (m, 2H), 1.75–1.88 (m, 1H), 1.20–1.40 (m, 2H), 0.96 (d, 3H, $J = 7.2$Hz). ^{13}C NMR ($CDCl_3$) δ 156.5; 137.3; 137.1; 129.2; 128.8; 128.1; 67.3; 48.1; 30.7; 30.2; 21.9. The enantiomeric excess was determined by HPLC on a Daicel Chiralcel OD-H (hexanes/IPA = 98:2). Retention times were: 31 min (major), 42 min (minor).
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22. Compounds **7** and **8** were not separable by chromatography (SiO_2). ^{1}H NMR ($CDCl_3$). Major (**7**): δ 7.36–7.26 (m, 5H), 5.33–5.30 (m, 1H), 5.08 (s, 2H), 4.80–4.70 (m, 1H), 4.30–4.10 (m, 1H), 2.07–1.13 (m, 10H), 0.87 (t, 3H, $J = 7.3$ Hz). Minor (**8**): 3.65–3.85 (m, 1H), 4.81 (s, 1H), 5.15 (s, 1H).