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Reversal of Diastereoselection in the Conjugate Addition of Cuprates to Unsaturated Lactams

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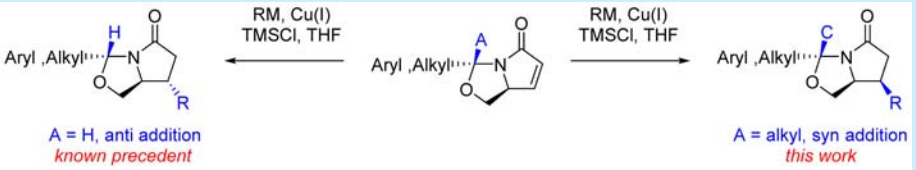
Supporting Information



ABSTRACT: We report that the stereochemical outcome of the conjugate addition of organocopper reagents to bicyclic α,β-unsaturated lactams derived from pyroglutaminol is determined by the nature of the aminal group. Bicyclic α,β-unsaturated lactams in which the aminal is derived from a ketone have been found to afford products of *syn* conjugate addition. By contrast, bicyclic α,β-unsaturated lactams in which the aminal is derived from an aldehyde afford products of *anti* conjugate addition. These remarkably different results obtained from very similar starting materials are unexpected.

The conjugate addition of organocopper reagents to α,β-unsaturated lactams, particularly those derived from pyroglutaminol (**1**, Figure 1), has been shown to be a valuable

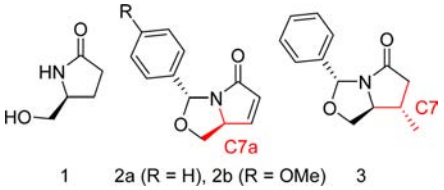


Figure 1. (*S*)-Pyroglutaminol (**1**), known bicyclic α,β-unsaturated aminal derivatives (**2**), and Me_2CuLi conjugate addition product (**3**).

tool for the highly diastereoselective synthesis of intermediates that have been subsequently elaborated to afford medicinal chemistry targets, natural products, and nonproteinogenic amino acids.[1] Of particular value in this regard are the bicyclic α,β-unsaturated lactams **2a** (R_1 = H) and **2b** (R_1 = OMe). The conjugate addition of organocopper reagents to these lactams, mediated by chlorotrimethylsilane (TMSCl), has been shown to occur in a manner *anti* to the stereocenter at C7α. This has been shown to be true for the addition of methyl- and vinyl-organocopper species to afford products such as **3**. The observed diastereoselection in these reactions has been ascribed to steric effects, explained as the methyl or vinyl group being preferentially delivered by the organocopper reagent to the sterically less hindered face of the olefin at C7.[2]

During the course of a recent medicinal chemistry program, we required intermediates derived from the bicyclic pyroglutaminol derivative **4** (Figure 2).[3] Having been provided with kilogram quantities of **4**, we prepared the bicyclic α,β-unsaturated lactam

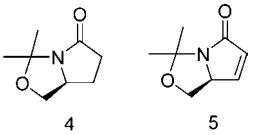


Figure 2. Saturated (**4**) and unsaturated (**5**) acetonide derivatives of (*S*)-pyroglutaminol.

5.[4] Although the conjugate addition of organocopper reagents to **5** was unknown, we fully expected the R group to be delivered by the organocopper reagent to the less hindered face of the olefin at C7, guided by the literature precedent of bicyclic α,β-unsaturated lactams such as **2a**. Indeed, the increased steric hindrance provided by the dimethyl group was anticipated to result in a further improvement in diastereoselection.

We were therefore surprised to find that the conjugate addition reaction of Me_2CuLi to **5**, in the presence of TMSCl, did not afford the expected *anti* addition product **6** but instead delivered the methyl group *syn* to the stereocenter at C7 to afford **7a**, as shown in Scheme 1.

The structure of **7a** was initially established by 2D NMR.[5] An authentic sample of **6** was prepared from **3**[6] and was demonstrated to be distinguishable from **7a** by ^{1}H NMR. The

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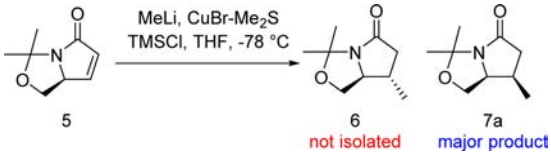
Scheme 1. Stereochemistry of Addition of Me_2CuLi to 5



assignment of **7a** was confirmed via an X-ray crystal structure (Figure 3, see also the Supporting Information).

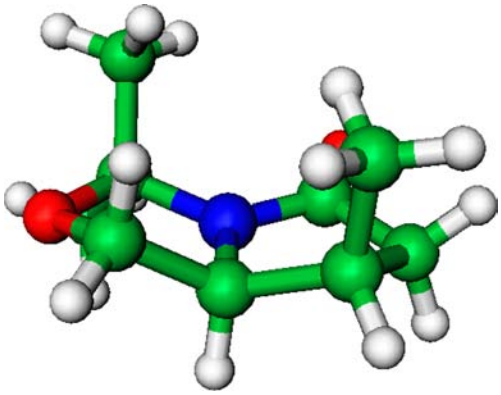


Figure 3. X-ray crystal structure of **7a**.

Further experiments demonstrated that other organocopper reagents, in the presence of TMSCl, likewise transferred the R group *syn* to the stereocenter at C7 with a high degree of diastereoselection (Table 1).

These results showed that the stereochemical outcome of the reaction was independent of the origin of the organometallic reagent used to prepare the organocopper species (Gilman or Grignard reagent). Additionally, the source of the copper(I) used to prepare the organocopper reagent made no apparent difference, with both diorganocuprates and mixed cyanocuprates affording similar results.

To confirm further the literature precedent reported previously with **2a**, we carried out similar transformations with **2b** to afford the conjugate addition products **8** (Table 2). As anticipated, in these reactions the R group was transferred *anti* to the stereocenter at C7 with a high degree of diastereoselection. The stereochemical outcome of the reaction was again independent of the origin of the organometallic reagent or the source of the copper(I) used. The nonidentity of the products *syn* **7** and *trans* **8** could also be established by removal of the aminal groups and comparison of the diastereomeric lactam alcohols.

We speculated that perhaps the diastereoselection observed with **2a** and **2b** might be due to delivery of the organocopper species to the *anti* face of the olefin by a complex between the copper species and the arene π-electrons. In that case, solvent effects might be expected to influence the stereochemical outcome of the reaction. However, the addition of an arene (anisole, 50% of solvent by volume) or a more coordinating ether solvent (DME, 50% of solvent by volume) resulted in no ablation of the diastereoselection observed when **2b** or **5** was treated with Me_2CuLi and TMSCl. The addition of 10 equiv of LiBr to the conjugate addition reaction mixtures also resulted in no change in the reaction outcome when either **2b** or **5** was treated with Me_2CuLi and TMSCl, suggesting that coordination of Me_2CuLi via the lithium ion was not a determining factor.

X-ray crystal structures of **2b** (Supporting Information) and **5** (Supporting Information) were obtained and showed no difference in the ground-state conformations of the bicyclic ring systems. The bicyclic rings were essentially superimposable. This eliminates steric differences in the starting materials, which suggests that the starting points for *syn* and *anti* addition are the same and that the differing reaction outcomes are the result of different transition-state energies and rate-limiting steps along the pathways to the products **7** and **8**.

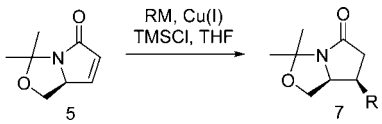
In an effort to understand the origin of the diastereoselection differences, we prepared some new bicyclic olefins **10a−c** from pyroglutaminol and the appropriate aldehyde or ketone dimethylacetal as shown in Scheme 2 and Table 3. In each case, the saturated bicyclic intermediates **9** were isolated as single diastereomers.

Exposure of the bicyclic olefins **10** to Me_2CuLi and TMSCl provided the conjugate addition products in good yields and with high levels of diastereoselection (Table 4). These results, taken together with the results obtained with **2b** and **5**, show that those bicyclic olefins formally derived from pyroglutaminol and an aldehyde (aldo-aminals **2a**,[7] **2b**, and **10c**) resulted in *anti* addition of the methyl group, while bicyclic olefins formally derived from pyroglutaminol and a ketone (keto-aminals **5**, **10a**, and **10b**) resulted in *syn* addition.

X-ray crystal structures of **12** (Supporting Information) and **17** (Supporting Information) were obtained, which further supported these structural assignments. The organocopper reagents derived from ethylmagnesium chloride or vinylmagnesium bromide and lithium (2-thienyl)cyanocuprate[8] gave similar levels of diastereoselection.

It is clear that the substituents on the aminal portion of the bicyclic olefin in **2a**,**b**, **5**, and **10a−c** control the stereochemical outcome of the organocopper addition. A mechanistic rationale for the observed stereochemical results that is based upon

Table 1. Organocopper Conjugate Additions to 5



entry	product	R	RM	Cu(I)[a]	yield[b] (%)	dr[c]
1	**7a**	Me	MeLi	$CuBr{\cdot}Me_2S$	82	26:1
2	**7b**	Et	EtMgCl	LiCu(2-Th)CN	90	30:1
3	**7c**	*n*-Pr	PrMgBr	CuCN	50	24:1
4	**7d**	vinyl	vinylMgBr	$CuBr{\cdot}Me_2S$	39	30:1

[a]Copper(I) source; LiCu(2-Th)CN = lithium (2-thienyl)cyanocuprate. [b]Yields are not optimized. [c]*Syn*/*anti* diastereomer ratio; determined by GC of crude reaction product.

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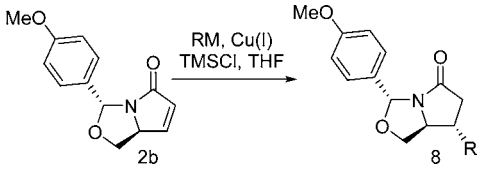
Table 2. Organocopper Conjugate Additions to 2b



entry	product	R	RM	Cu(I)[a]	yield[b] (%)	dr[c]
1	**8a**	Me	MeLi	CuBr·Me_2S	98	1:30
2	**8b**	Et	EtMgCl	LiCu(2-Th)CN	89	1:25
3	**8c**	*n*-Pr	PrMgBr	CuCN	65	1:25
4	**8d**	vinyl	vinylMgBr	CuBr·Me_2S	71	1:26

[a]Copper(I) source; LiCu(2-Th)CN = lithium (2-thienyl)cyanocuprate. [b]Yields are not optimized. [c]*Syn/anti* diastereomer ratio; determined by GC of crude reaction product.

Scheme 2. Preparation of Bicyclic Olefins 10a−c

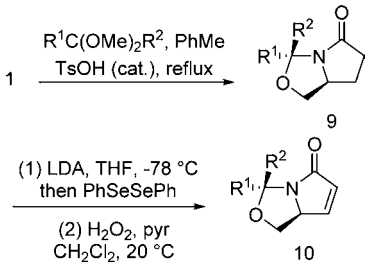
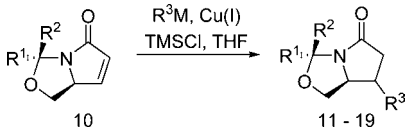


Table 3. New Bicyclic Derivatives of (*S*)-Pyroglutaminol

entry	compound	R^1	R^2	yield (%)	mp (°C)
1	**9a**	$-(CH_2)_5-$		63	77−79
2	**9b**	4-(MeO)C_6H_4	Me	47	oil
3	**9c**	CMe_3	H	40	oil
4	**10a**	$-(CH_2)_5-$		55	46−48
5	**10b**	4-(MeO)C_6H_4	Me	74	30−33
6	**10c**	CMe_3	H	71	oil

Table 4. Organocopper Conjugate Additions to 10a−c



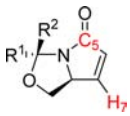
entry	**10**	R^3	R^3 M	product	yield[a] (%)	dr[b]
1	**10a**	Me	MeLi[c]	**11**	47	27:1
2	**10a**	Et	EtMgCl[d]	**12**	49	30:1
3	**10a**	vinyl	vinylMgBr[e]	**13**	57	14:1
4	**10b**	Me	MeLi	**14**	58	9:1
5	**10b**	Et	EtMgCl	**15**	86	9:1
6	**10b**	vinyl	vinylMgBr	**16**	30	3:1
7	**10c**	Me	MeLi	**17**	63	1:18

[a]Yields are not optimized. [b]*Syn/anti* diastereomer ratio; determined by GC of crude reaction product. [c]Used with CuBr Me_2S. [d]Used with lithium (2-thienyl)cyanocuprate. [e]Used with CuCN.

delivery of the organocopper species to the *anti* face of the olefin in **2b** by a complex between the copper species and the arene π-electrons can be firmly excluded based on the results obtained with **10b** and **10c**. Similarly, a mechanistic rationale for the observed stereochemical results that is based solely upon steric control can also be discounted. In the case of keto-aminals (**5**, **10a**, and **10b**), the organocopper reagent is delivered to the *syn* face of the olefin despite the steric hindrance offered by the methyl groups (**5**, **10b**) or cyclohexyl group (**10a**). By contrast, for aldo-aminals (**2a**, **2b**, and **10c**), the organocopper reagent is delivered to the *anti* face of the olefin despite the lack of steric bulk offered by the aminal hydrogen substituent.

Possible clues to the origin of this mechanistic discrepancy may be found in the ^1H and ^{13}C NMR spectra of the olefin starting materials. In particular, the chemical shifts of the proton at C7 and the carbonyl carbon at C5 may be significant (Table 5).

Table 5. Comparison of Selected NMR and Calculated LUMO Data for α,β-Unsaturated Bicyclic Lactams



compd	R^1	R^2	δ H-7[a]	δ C=O[b]	LUMO[c]
2b	4-(MeO)C_6H_4	H	7.27	176.87	−1.66
10c	CMe_3	H	7.23	176.35	−1.64
5	Me	Me	7.07	172.12	−1.56
10a	$-(CH_2)_5-$		7.07	172.05	−1.53
10b	4-(MeO)C_6H_4	Me	7.14	173.20	−1.59
cyclopentenone			7.62	210.61	−1.71

[a]Chemical shift of proton at C7 in ppm. [b]Chemical shift of carbonyl carbon in ppm. [c]Calculated LUMO of olefin in eV.[9]

In keto-aminals (**5**, **10a**, and **10b**), the ^1H NMR chemical shift of the proton at C7 occur upfield relative to the same protons in the aldo-aminals (**2b**, **10c**). Also, in keto-aminals, the ^{13}C NMR chemical shift of the carbonyl carbon at C5 occurs upfield relative to the carbonyl carbons in aldo-aminals. Taken together, these results suggest that the aminals that are derived from aldehydes are more similar to cyclopentenone[10] and that the canonical resonance form **A** (Figure 4) contributes more to the aldo-aminals, while the resonance form **B** contributes more to the keto-aminals.[11] The calculated LUMO of the olefin are in line with these observations. Although these differences are observed at positions relatively distant from the aminal group, it is

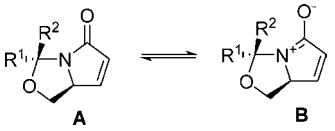


Figure 4. Resonance forms of bicyclic unsaturated lactams.

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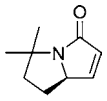
nonetheless clear that the substituents on the aminal carbon at C3 exert a significant influence upon the carbonyl group and olefin in the α,β-unsaturated lactam. Whether these differences contribute to the observed stereochemical outcomes is not clear but seems to be unlikely.

We found that keto-aminal α,β-unsaturated lactams such as **5** resisted cyclopropanation upon treatment with the sulfur ylides derived from trimethylsulfonium iodide and trimethylsulfoxonium iodide, whereas under the same conditions, **2a** and **2b** underwent cyclopropanation readily.[12] These results are further consistent with the suggestion that the olefin in keto-aminals such as **5** is less polarized and less electrophilic than the olefin in aldo-aminals such as **2a** and **2b**.

Study of the α,β-unsaturated lactam **18** (Figure 5) was undertaken to try to understand these results further. This



18

Figure 5. α,β-Unsaturated lactam lacking an aminal functional group.

compound exhibited ^{1}H and ^{13}C spectra similar to those of **5** (δ H-7 7.05, δ C=O 171.59). Unlike **5**, conjugate addition of Me_2CuLi to **18** could not be effected under the same conditions, suggesting that perhaps prior coordination of the organocopper reagent to the aminal oxygen in **5** is a prerequisite for successful reaction.

In conclusion, we show that the diastereoselection observed during the TMSCl-mediated addition of organocopper reagents to bicyclic α,β-unsaturated lactams such as **2** and **5** is ultimately dictated by the structure of the aminal group. Keto-aminals afford products of *syn* addition, while aldo-aminals result in *anti* addition products. These results are at odds with the currently proposed rationale, which concludes that the diastereoselection is solely the result of steric considerations. The origin of the diastereoselection observed with keto-aminals such as **5**, **10a**, and **10b** remains an open question.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02533.

Experimental procedures and characterization for **5**, **6**, **9a−c**, **10a−c**, and **18**; general procedures and characterization for **7a−c**, **8a−c**, and **11−17** (PDF)
X-ray data for **2b** (CIF)
X-ray data for **5** (CIF)
X-ray data for **7a** (CIF)
X-ray data for **12** (CIF)
X-ray data for **14** (CIF)
X-ray data for **17** (CIF)

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Notes

The authors declare no competing financial interest.

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(3) This compound has been extensively used as a synthon for the preparation of intermediates functionalized at C6 by enolate formation and trapping with an electrophile. The functionalization of C6 usually occurs with very acceptable levels of diastereoselection, and separation of the diastereomeric products is often easily accomplished. See: (a) Doyle, M. P.; Hu, W.; Phillips, I. M.; Moody, C. J.; Pepper, A. G.; Slawin, A. M. Z. *Adv. Synth. Catal.* **2001**, *343*, 112. (b) Davies, S. G.; Dixon, D. J.; Doisneau, G. J.-M.; Prodger, J. C.; Sanganee, H. J. *Tetrahedron: Asymmetry* **2002**, *13*, 647.

(4) This compound has been reported once previously, in which it underwent photocycloaddition with ethylene to afford a cyclobutane: Tsujishima, H.; Nakatani, K.; Shimamoto, K.; Shigeri, Y.; Yumoto, N.; Ohfune, Y. *Tetrahedron Lett.* **1998**, *39*, 1193.

(5) These experiments showed a positive NOE correlation between the protons on the 7-methyl group and the protons on the CH_2O carbon at C1, as well as a lack of NOE correlation between the protons on the 7-methyl group and the proton at the 7α stereocenter.

(6) This was conducted by cleavage of the 4-methoxybenzylidene group (cat. TsOH, MeCN, H_2O) followed by acetonide formation (cat. TsOH, Me_2CO, 2-methoxypropene).

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(9) Calculations were performed using Spartan '14 v1.1.9 released Aug 27, 2014, from Wavefunction. Calculations were done at the DFT EDF2 6-31+G* level of theory.

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