COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Unprecedented copper-catalyzed asymmetric conjugate addition of organometallic reagents to α,β-unsaturated lactams†

Mauro Pineschi,*[a] Federica Del Moro,[a] Francesca Gini,[ab] Adriaan J. Minnaard[b] and Ben L. Feringa[b]

[a] *Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy. E-mail: pineschi@farm.unipi.it; Fax: +3905043321*

[b] *Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747, AG Groningen, The Netherlands*

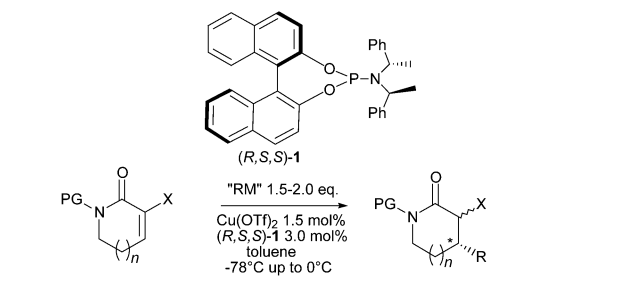
Received (in Cambridge, UK) 11th March 2004, Accepted 6th April 2004
First published as an Advance Article on the web 28th April 2004

For the first time, an excellent enantioselectivity has been obtained in the conjugate addition of hard organometallic reagents to α,β-unsaturated lactams bearing appropriate protecting–activating groups on the nitrogen.

The asymmetric conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is one of the most useful methods to assemble carbon–carbon bonds in organic chemistry, and several highly enantioselective processes have been developed.[1] In the case of α,β-unsaturated lactams, Hayashi has recently described a highly enantioselective Rh(I)/BINAP catalyzed 1,4-addition of arylboronic reagents to cyclic 5,6-dihydro-2(1*H*)-pyridinones.[2] Using a different approach, Buchwald very recently developed a catalytic enantioselective conjugate reduction of five- and six-membered α,β-unsaturated lactams.[3] However, the stereoselective introduction of a carbon–carbon bond in the β-position of a lactam is mostly based on the use of stoichiometric amounts of chiral auxiliaries[4] or reagents.[5] Chiral copper complexes with non-racemic BINOL-based phosphoramidites have proved to be excellent catalysts for the conjugate addition of dialkylzinc reagents to enones.[6] To the best of our knowledge, the catalytic enantioselective 1,4-addition of hard alkyl metals to α,β-unsaturated lactams has not been described. Here we wish to report an unprecedented enantioselective copper-phosphoramidite catalyzed alkylation of α,β-unsaturated lactams with dialkylzincs and trialkylaluminium reagents.

It is known that *N*-alkyl-α,β-unsaturated lactams without an additional withdrawing group in the α-position possess an inherently low reactivity.[7] Consistent with this observation, we found that *N*-methyl- and *N*-benzyl-5,6-dihydro-2(1*H*)-pyridinones **2a** and **2b** do not react with Et_2Zn in the presence of catalytic amounts of $Cu(OTf)_2$/(*R*,*S*,*S*)-**1** (Scheme 1).[8]

The contemporary introduction of a carbomethoxy group in the α-position and a carbamate protecting group for the nitrogen, as in compound **2c**, was able to overcome this low reactivity. In this case



2a, *n*=1, PG=CH_2Ph, X=H
2b, *n*=1, PG=Me, X=H
2c, *n*=1, PG=CO_2Ph, X=CO_2Me
2d, *n*=1, PG=COPh, X=H
2e, *n*=1, PG=Cbz, X=H
2f, *n*=1, PG=CO_2Ph, X=H
3, *n*=0, PG=Boc, X=H

4, *n*=1, PG=CH_2Ph, R=Et, X=H
5, *n*=1, PG=CO_2Ph, R=Et, X=CO_2Me
6, *n*=1, PG=COPh, R=Et, X=H
7, *n*=1, PG=Cbz, R=Et, X=H
8a, *n*=1, PG=CO_2Ph, R=Et, X=H
8b, *n*=1, PG=CO_2Ph, R=Bu, X=H
8c, *n*=1, PG=CO_2Ph, R=Me, X=H
9, *n*=0, PG=Boc, R=Et, X=H

Scheme 1

† Electronic supplementary information (ESI) available: experimental procedures, enantioselectivity determinations and characterization data for all new compounds. See http://www.rsc.org/suppdata/cc/b4/b403793f/

a very fast reaction occurred at −78 °C even in the absence of the catalyst and invariably the racemic *trans* adduct **5** was obtained as the major product. To minimize the uncatalyzed background reaction, the sole use of a protecting–activating group for the nitrogen proved to be sufficient (Table 1).

The Cu(II)/(*R*,*S*,*S*)-**1** catalysed addition of Et_2Zn to the *N*-benzoyl lactam **2d** gave 83% conversion in 4 h from −78 °C up to 0 °C and 4-ethyl-2-piperidinone **6** was obtained with 26% ee (entry 1, Table 1). The Cbz-protected lactam **2e** underwent a clean addition reaction, with a complete conversion in 3 h from −78 °C up to 0 °C, to provide the corresponding β-ethyl substituted lactam **7** with 75% ee (entry 2).

During the search for a more enantioselective reaction, the *N*-carbophenoxy group was found to be superior to all the other protecting–activating groups in terms of both reactivity and enantioselectivity. Indeed substrate **2f** gave the corresponding β-ethyl substituted lactam **8a** with 95% ee and complete conversion in 2 h (entry 3). Similarly, the reaction of **2f** with Bu_2Zn was completed in 4 h from −78° to 0 °C and afforded the corresponding β-butylated lactam **8b** with a high ee (entry 4). Unfortunately, the easily accessible *N*-Boc-dihydropyrrol-2-one[10] **3** gave a more complex reaction mixture with dialkylzinc reagents and the corresponding β-ethylated addition product **9** was found to be not entirely stable under standard chromatographic purification on SiO_2 (entry 5).[11] δ-Lactams **2d–f** and *N*-Boc-γ-lactam **3** were not alkylated by Me_2Zn under our reaction protocol even using prolonged reaction times and a large excess of the reagent (data not shown in Table 1). Therefore, we decided to change the primary organometallic reagent from the poorly reactive Me_2Zn to Me_3Al in order to address the asymmetric formation of β-methylated lactams.

Trialkylaluminiums are interesting organometallic reagents because they are produced on an industrial scale and possess a high chemoselectivity and a low toxicity.[12] Only a few examples of enantioselective conjugate additions using trialkylaluminium reagents have been reported,[13] and to the best of our knowledge,

Table 1 Enantioselective conjugate addition of organometallic reagents ("RM") to α,β-unsaturated lactams catalysed by (*R*,*S*,*S*)-**1**/$Cu(OTf)_2$[a]

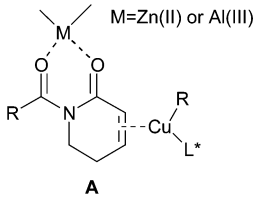
Entry	Lactam	"RM"	Time/*T*	Conv.[b]	Ee (%)[c]
1	**2d**	Et_2Zn	4 h/up to 0 °C	83 (50)	26
2	**2e**	Et_2Zn	3 h/up to 0 °C	100 (70)	75
3	**2f**	Et_2Zn	2 h/up to −50 °C	100 (65)	**95**
4	**2f**	Bu_2Zn	4 h/up to 0 °C	100 (52)	> 90[d]
5	**3**	Et_2Zn	4 h/up to 0 °C	90 (15)	35
6	**2f**	Me_3Al	2 h/up to 0 °C	100 (78)	68
7	**2f**	Et_3Al	1 h/up to −30 °C	100 (88)	28
8	**3**	Et_3Al	2 h/up to 0 °C	95 (25)[e]	3

[a] *Conditions*: all reactions were run in accordance with the typical procedure.[9] [b] Conversions are determined by ^1H NMR examination of the crude reaction mixture. Isolated yields after chromatographic purification (SiO_2) are reported in parentheses. [c] Determined by HPLC on Daicel Chiralcel OB-H or OD-H columns. [d] Determined after zinc enolate trapping with acetaldehyde. [e] Isolated yield after transformation into the corresponding *N*-benzyl derivative.[11]

DOI: 10.1039/b403793f

unsaturated lactams have never been used as substrates for this reaction. The $Cu(OTf)_2$–**1** catalysed addition of Me_3Al to lactam **2f** proceeded very cleanly in 2 h to give the corresponding methylated addition product **8c**, with a good enantioselectivity of 68% (entry 6). When the reaction was carried out with Et_3Al it was possible to obtain compound **8a** with a high yield, albeit with a modest 28% ee (entry 7). Also with the γ-lactam **3**, the use of Et_3Al proved to be less enantioselective than Et_2Zn (entry 8).

It is reasonable to assume that the different reactivity displayed by *N*-alkyl- and *N*-carbonyl-δ-lactams with dialkylzinc and organoaluminium reagents is due to the greater electron withdrawing ability of the latter protecting–activating group, which renders the reactive β-carbon more electrophilic in nature. Furthermore, a chelation by the metal ions of the two carbonyl oxygens, as shown in **A** (Fig. 1), might be responsible for a further double bond activation[14] and for a beneficial reduction of the conformational mobility of the substrate.

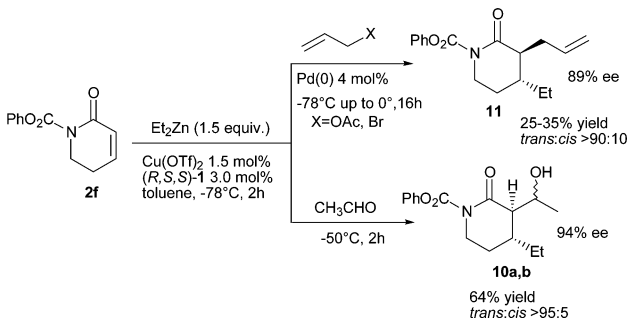


A

Fig. 1 Plausible intermediate metal-chelated structure.

Conjugate addition to unsaturated ketones, followed by trapping of the zinc enolate with an electrophile, is an efficient method to build up more complex molecules.[15] Here we report that also the intermediate zinc enolate derived from the conjugate addition of Et_2Zn to unsaturated lactam **2f** can be trapped with acetaldehyde at −50 °C to give the new *trans*-3,4-disubstituted 2-piperidinone **10a,b** as an inseparable mixture of aldols with 94% ee (Scheme 2).[16] Furthermore, the same intermediate can be trapped in a one-pot procedure by allyl bromide or allyl acetate and 4 mol% of $Pd(PPh_3)_4$ to deliver piperidinone **11** with 89% ee, albeit with 25–35% isolated yield.[17] It should be noted that substituted six-membered lactams can also serve as precursors to enantiomerically enriched piperidines which are important structural motifs in pharmaceuticals.[18]

In conclusion, we have reported the first catalytic asymmetric alkylation of α,β-unsaturated lactams with hard organometallic reagents. The reaction gives access to new β-alkyl-substituted δ-lactams in an enantioenriched form. Further findings established that the reaction is also amenable to three-component processes to give α,β-disubstituted lactams.



Scheme 2

We gratefully acknowledge funding by M.I.U.R. (PRIN 2002) and by the University of Pisa.

Notes and references

1 K. Tomioka and Y. Nagaoka, in *Comprehensive Asymmetric Catalysis*, E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds., Springer-Verlag, Berlin, Heidelberg, 1999; **Vol. 3**; Chapter 31.1.

2 T. Senda, M. Ogasawara and T. Hayashi, *J. Org. Chem.*, 2001, **66**, 6852 and references therein.

3 G. Hughes, M. Kimura and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 11253.

4 (*a*) A. I. Meyers and L. Snyder, *J. Org. Chem.*, 1993, **58**, 36; (*b*) M. Amat, M. Pérez, N. Llor and J. Bosch, *Org. Lett.*, 2002, **4**, 2787; (*c*) J. Cossy, O. Mirguet, D. Gomez Pardo and J.-R. Desmurs, *Tetrahedron Lett.*, 2001, **42**, 7805.

5 (*a*) S. Hanessian, A. Gomtsyan and N. Malek, *J. Org. Chem.*, 2000, **65**, 5623; (*b*) S. H. Lim and P. Beak, *Org. Lett.*, 2002, **4**, 2657.

6 For overviews of phosphoramidites in catalytic asymmetric conjugate additions, see: (*a*) B. L. Feringa, *Acc. Chem. Res.*, 2000, **33**, 346; (*b*) A. Alexakis and C. Benhaim, *Eur. J. Org. Chem.*, 2002, 3221.

7 M. Amat, N. Llor, J. Bosch and X. Solans, *Tetrahedron*, 1997, **53**, 719 and references therein.

8 A useful conversion of compounds **2a** can only be obtained by the use of THF as the reaction solvent (see Supporting Information). However, the corresponding adduct **4** was obtained as a racemate.

9 *Typical procedure*: a solution of $Cu(OTf)_2$ (2.5 mg, 0.0069 mmol) and (*R*,*S*,*S*)-**1** (7.5 mg, 0.00138 mmol) in anhydrous toluene (1 ml) was stirred at room temperature for 40 min. The colorless solution was cooled to −78 °C and subsequently a solution of the lactam (0.46 mmol) in the minimal amount of toluene (or CH_2Cl_2 for **2f**) and 0.69 mmol of R_2Zn or R_3Al (0.92 mmol) were added. The reaction was followed by TLC analysis and quenched with saturated aqueous NH_4Cl after the times and at the temperatures indicated in Table 1.

10 G. Rassu, G. Casiraghi, P. Spanu, L. Pinna, G. Gasparri Fava, M. Belicchi Ferrari and G. Pelosi, *Tetrahedron: Asymmetry*, 1992, **3**, 1035.

11 For preparative and enantioselectivity determination, **9** was transformed into the corresponding *N*-benzyl derivative.

12 J. Westermann and K. Nickisch, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1368.

13 (*a*) L. Su, X. Li, W. L. Chan, X. Jia and A. S. C. Chan, *Tetrahedron Lett.*, 2003, **14**, 1865; (*b*) S. M. Bennett, S. M. Brown, J. P. Muxworthy and S. Woodward, *Tetrahedron Lett.*, 1999, **40**, 1767; (*c*) M. Dieguez, S. Deerenberg, O. Pamies, C. Claver, P. W. N. M. van Leeuwen and P. Kamer, *Tetrahedron: Asymmetry*, 2000, **11**, 3161.

14 For a discussion of the acceleration of conjugate addition reactions by Lewis acids, see: E. Nakamura, M. Yamanaka and S. Mori, *J. Am. Chem. Soc.*, 2000, **122**, 1826 and references therein.

15 For examples, see: (*a*) B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos and A. H. M. de Vries, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2620; (*b*) O. Knopff and A. Alexakis, *Org. Lett.*, 2002, **4**, 3835.

16 The mixture of aldols was oxidized to the corresponding ketone (see Supporting Information). Also *N*-Boc-dihydropyrrol-2-one can be used in analogous three-component aldol reactions, although the yields are lower.

17 For a tandem conjugate addition–allylation reaction of enones, see: R. Naasz, L. A. Arnold, M. Pineschi, E. Keller and B. L. Feringa, *J. Am. Chem. Soc.*, 1999, **121**, 1104.

18 For a recent review of methods for the stereoselective synthesis of piperidines, see: S. Laschat and T. Dickner, *Synthesis*, 2000, 1781.

Typeset and printed by Black Bear Press Limited, Cambridge, England