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Copper-Catalyzed Asymmetric Conjugate Addition of Alkenyl- and Alkylalanes to α,β-Unsaturated Lactams

Pierre Cottet, Daniel Müller, and Alexandre Alexakis*

Department of Organic Chemistry, University of Geneva, Quai Ernest Ansermet 30, CH-1211 Geneva 4, Switzerland

alexandre.alexakis@unige.ch

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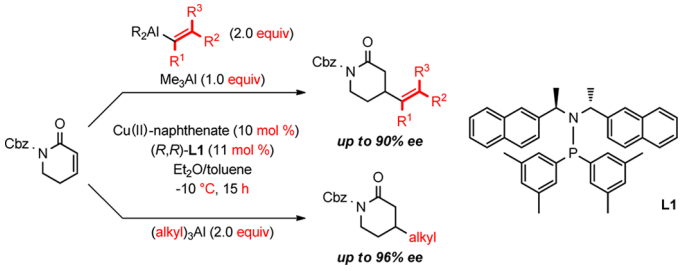
ABSTRACT



Alkenyl and alkyl groups have been successfully introduced to six-membered α,β-unsaturated lactams via a copper-catalyzed asymmetric 1,4-addition of the corresponding alanes. Moderate to good yields and good to excellent enantioselectivities are achieved by using a combination of the very cheap copper(II) naphthenate and a readily available phosphine amine ligand. The creation of an all-carbon quaternary stereogenic center, via Michael addition to a trisubstituted conjugated lactam, is also disclosed for the first time.

Among the main reactions in organic synthesis, the asymmetric conjugate addition (ACA) of organometallic species is one of the most powerful tools for enantioselective C−C bond formation. Highly effective Cu- and Rh-catalyzed procedures have been reported on a wide range of Michael acceptors and have been applied in the total synthesis of natural products.[1] However, some Michael acceptors remain challenging substrates in ACA reactions, such as α,β-unsaturated lactams, on which most efforts have been dedicated to the introduction of aryl substituents. In 2001, Hayashi was the first to describe the highly enantioselective Rh-catalyzed 1,4-addition of arylboron reagents to 5,6-dihydro-2(1*H*)-pyridinones.[2] Later, various types of aryl nucleophiles were successfully employed: arylsiloxanes,[3] aryl[2-(hydroxymethyl)phenyl]dimethylsilanes,[4] 2-heteroarylzinc reagents,[5] and arylboronic acids.[6] In 2004, Feringa reported the ACA of nonstabilized alkyl nucleophiles to α,β-unsaturated lactams, allowing for the formation of enantioenriched β-alkyl-substituted δ-lactams.[7] Nevertheless, a limited number of alkyl groups could be introduced in high enantioselectivity. Moreover, the use of alkenyl nucleophiles in the context of Michael addition to conjugated lactams is scarce in the literature.[6b] Based on our experience in the field of alkenyl alanes chemistry,[8] we decided to

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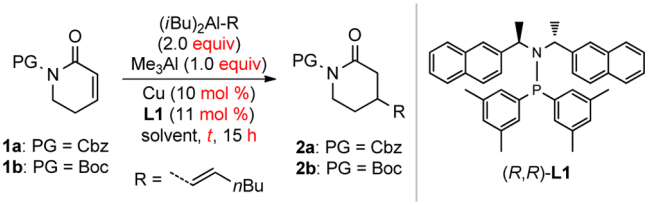
reinvestigate α,β-unsaturated lactams as substrates for ACA reactions (during the course of our study, Feng, Lin, et al. published the enantioselective rhodium-catalyzed 1,4-addition of potassium alkenyltrifluoroborates to α,β-unsaturated lactams).[9] Herein, we describe the asymmetric copper-catalyzed Michael addition of alkenyl- and alkylalanes to six-membered conjugated lactams, leading to valuable building blocks for the preparation of optically active nitrogen-containing heterocycles.

Very recently, we reported optimized conditions for the copper-catalyzed 1,4-addition to 2,3-dehydro-4-piperidones.[8g] The reaction, promoted by a chiral monodentate phosphine amine−copper complex, is highly enantioselective, whatever the nature of the organoaluminum reagent (alkenyl, alkyl, and aryl). Assuming that 2,3-dehydro-4-piperidones and α,β-unsaturated lactams might have similar reactivity, we decided to start with the same reaction conditions in this study, on **1a** as substrate of choice (prepared from the commercially available δ-valerolactam, by a three steps sequence: protection, α-selenation, elimination).[7,10] According to the study of Feringa, the right protecting-activating group had to be selected in his case, in order to get full conversion and high enantioselectivity.[7] The benzyloxycarbonyl (Cbz) group was chosen for our test substrate **1a** because it could be cleaved without touching the lactam function, contrary to other protecting groups.[11] As shown in Table 1, the original conditions developed for 2,3-dehydro-4-piperidones could be applied on **1a**, affording the desired product **2a** with acceptable isolated yield (58%) and a promising enantioselectivity of 80% (entry 1). The reaction was catalyzed by the combination of copper(II) naphthenate (CuNp) and a SimplePhos ligand **L1**, which can be easily prepared on a multigram scale.[8f] Coactivation with Me_3Al was also employed for the reaction to proceed, as previously reported for challenging substrates in the context of tandem hydroalumination/Cu-catalyzed 1,4-additions.[8f,g] The enantiomeric excess could be increased by lowering the reaction temperature. Unfortunately, it caused a decrease of the isolated yield, even if the reactions went to completion in both examples (entries 2 and 3). Running the reaction in toluene (entry 4) or THF (entry 5) led mainly to a degradation of the starting material. Interestingly, good results were obtained when the lactam **1a** was added to the reaction mixture in a toluene solution. These conditions allowed for the formation of the 1,4-adduct in acceptable isolated yield (53%) and good enantioselectivity (86%) while preserving the reaction temperature at a more practical value (entry 6).

Table 1. Optimisation of the Reaction Conditions[a]



entry	lactam	Cu salt[b]	solvent	temp (°C)	yield[c] (%)	ee[d] (%)
1	**1a**	CuNp	Et_2O	−10	58	80
2	**1a**	CuNp	Et_2O	−30	55	84
3	**1a**	CuNp	Et_2O	−50	42	89
4[e]	**1a**	CuNp	toluene	−10		
5[e]	**1a**	CuNp	THF	−10		
6	**1a**	**CuNp**	**Et_2O/toluene**	**−10**	**53**	**86**
7	**1b**	CuNp	Et_2O/toluene	−10	42	66
8	**1a**	CuTC	Et_2O/toluene	−10	50	87

[a] Reactions performed on a 0.2 mmol scale, under an Ar atmosphere. Conversion = 100%, determined by ^1H NMR of the crude mixture. [b] CuNp = solution of copper(II) naphthenate in pentane; CuTC = Cu(II) thiophene-2-carboxylate. [c] Isolated yields. [d] Determined by supercritical fluid chromatography (SFC) on a chiral stationary phase. [e] A degradation of the starting material was mainly observed by ^1H NMR of the crude reaction mixture.

Then, lactam **1b**,[12] bearing a *tert*-butoxycarbonyl (Boc) moiety as an alternative protecting group, was subjected to this Michael addition. Unfortunately, the corresponding product **2b** was isolated in lower yield and poorer enantioselectivity (entry 7). Finally, the reaction was performed in the presence of copper(I) thiophene-2-carboxylate (CuTC) on **1a** (entry 8). This copper salt and CuNp gave similar results. However, the reaction is slightly cleaner in the presence of the latter. Moreover, the fact that CuNp can be used as a stock solution and is the cheapest commercially available organic copper source urged us to choose CuNp for the following study.

With the optimized conditions in hand, we studied the nucleophile scope of the reaction (Table 2). Efficient methodologies were selected for the preparation of the requisite aluminum-based reagents: either by hydroalumination of terminal alkynes with DIBAL-H (method A), which can afford the branched vinylalane in the presence of the right Ni complex (method C) or by lithium−halogen exchange from the corresponding alkenyl bromide, followed by transmetalation with Me_2AlCl (method B).[13] As shown in Table 2, alkyl β-substituted alkenylalanes, made via hydroalumination with DIBAL-H, could be introduced to **1a** effectively, providing the desired 1,4-adducts in good enantioselectivities and practical yields (entries 1 and 3), which could be improved by increasing the reaction scale (entry 2). However, a more sterically demanding alkenylalane, bearing a *tert*-butyl group, led to a lower

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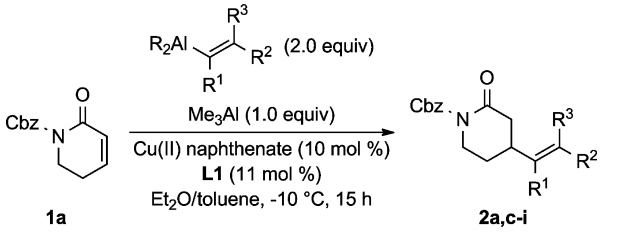
(13) For details about these methodologies (advantages and limitations), see ref 8g and references cited therein.

Table 2. Cu-Catalyzed ACA of Alkenylalanes to Lactam **1a**[a]



	alkenylalane					
entry	method[b]	R^1	R^2	R^3	yield[c] (%)	ee[d] (%)
1	A[e]	H	*n*-Bu	H	53 (**2a**)	86
2[f]	A[e]	H	*n*-Bu	H	70 (**2a**)	86
3	A[e]	H	Cy	H	54 (**2c**)	82
4	A[e]	H	*t*-Bu	H	66 (**2d**)	72
5[f]	A[e]	H	$(CH_2)_3Cl$	H	58 (**2e**)	84
6	B[g]	H	Ph	H	69 (**2f**)	90
7	B[g]	Me	H	H	54 (**2g**)	74
8	C[h]	*n*-Bu	H	H	30 (**2h**)	51
9[i]	A[e]	H	H	CH_2O-*t*-Bu	47 (**2i**)	12

[a] Reactions performed on a 0.2 mmol scale, under an Ar atmosphere. Conversion = 100%, determined by ^{1}H NMR or TLC. [b] The letter indicated refers to the general procedure which was used for the preparation of the corresponding alane; see the Supporting Information for details. [c] Isolated yields. [d] Determined by SFC on a chiral stationary phase. [e] Alanes made by hydroalumination of terminal alkynes with DIBAL-H (R = *i*Bu).[8g] [f] Reaction performed on a 0.4 mmol scale. [g] Alanes made by lithium−halogen exchange from the corresponding alkenyl bromides, followed by transmetalation with Me_2AlCl (R = Me).[8c,g] [h] Alane made by Ni-catalyzed α-hydroalumination of 1-hexyne (R = *i*Bu).[8g,14] [i] Et_2O was replaced by THF, 20 mol % of Kubas salt $[Cu(MeCN)_4]BF_4$, and 22 mol % of ligand **L1** were used; 3 equiv of alane was added.[8g]

enantiomeric excess (entry 4). Interestingly, good results were obtained with a functionalized alane, allowing further transformations on the corresponding product (entry 5). The lithium−bromine exchange/transmetalation sequence was used to generate the pure *trans*-styryl alane, which underwent the ACA with good yield and good enantioselectivity (entry 6). The same strategy was used to prepare isopropenylalane from 2-bromopropene. It went through a clean 1,4-addition, albeit with a relatively lower level of stereoinduction (entry 7). Then, a second alkyl α-substituted alkenylalane was made by Ni-catalyzed α-hydroalumination of 1-hexyne.[8g,14] However, the corresponding product **2h** was obtained in a low isolated yield and a poor enantioselectivity (entry 8). The presence of THF, required for the preparation of this aluminum reagent, should be incompatible with the catalytic system (as seen in Table 1, entry 5). The steric hindrance of the α-substituted alkenyl alane could also be responsible for the low selectivity. In addition, the presence of Ni derivatives in the reaction mixture may not explain this result because it has been shown that nickel salts could catalyze with a very low efficiency the conjugate addition of alkenylalanes to 2,3-dehydro-4-piperidones.[8g] Finally, the catalytic system proved to be

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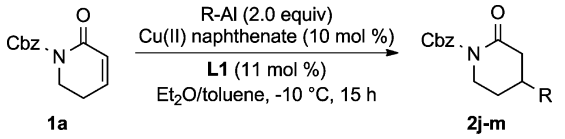
Table 3. Cu-Catalyzed ACA of Alkyl- and Arylalanes to Lactam **1a**[a]



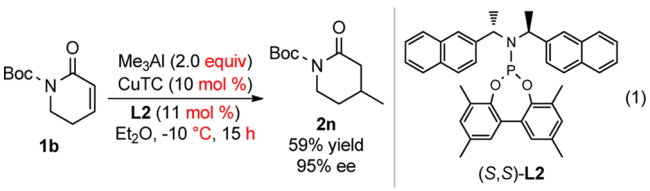
entry	R	yield[b] (%)	ee[c] (%)
1	Me[d]	54 (**2j**)	94
2	Et[d]	45 (**2k**)	96
3	*i*-Bu[d]	42 (**2l**)	86
4	Ph[e]	51 (**2m**)	86

[a] Reactions performed on a 0.2 mmol scale, under an Ar atmosphere. Conversion = 100%, determined by ^{1}H NMR or TLC. [b] Isolated yields. [c] Determined by SFC on a chiral stationary phase. [d] Commercially available R_3Al were used. [e] Alane made by lithium−halogen exchange from bromobenzene, followed by transmetalation with Me_2AlCl; coactivation with 1.0 equiv of Me_3Al.

inappropriate to promote the 1,4-addition of a Z-alkenylalane, prepared by hydroalumination of *tert*-butyl propargyl ether.[8g,15] Under the standard reaction conditions, Me and *i*-Bu transfer were mainly observed. The same issue was encountered with 2,3-dehydro-4-piperidones, and special conditions were developed (Et_2O was replaced by THF to suppress Me- and *i*-Bu-transfer; 20 mol % of Kubas salt $[Cu(MeCN)_4]BF_4$ and 22 mol % of ligand **L1** were used; 3 equiv of alane was added).[8g] These modifications allowed us actually to isolate 47% of the desired product **2i**. Unfortunately, almost no enantioselectivity was observed (entry 9).

Since a limited number of alkyl chains have been successfully introduced selectively to α,β-unsaturated lactams,[7] it was interesting to test our conditions in the presence of various trialkylaluminum reagents (Table 3). To our delight, under the same conditions, the reaction afforded the product **2j** in a high enantioselectivity of 94%, which was a great improvement for the methyl group (entry 1). The reaction worked equally well with triethylaluminum (entry 2). A good enantiomeric excess was obtained for the isobutyl derivative **2l** (entry 3). The reaction was also extended to the 1,4-addition of an arylalane, leading to the product **2m** in a moderate yield and a good enantioselectivity (entry 4).

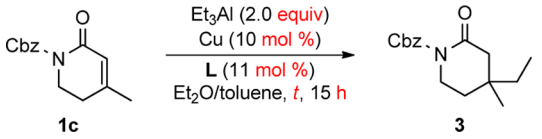
Interestingly, the CuTC/**L2** complex, known to be highly efficient for Michael additions with organoaluminum reagents,[8b,c] gave excellent results for the 1,4-addition of trimethylaluminum to the *N*-Boc derivative **1b** (eq 1).[16]



(1)

Finally, we investigated the ability of our catalytic system for promoting ACA to trisubstituted conjugated lactams. The substrate **1c** was prepared by protection of the

Table 4. Cu-Catalyzed ACA of Triethylaluminum to the β-Substituted Conjugated Lactam **1c**[a]



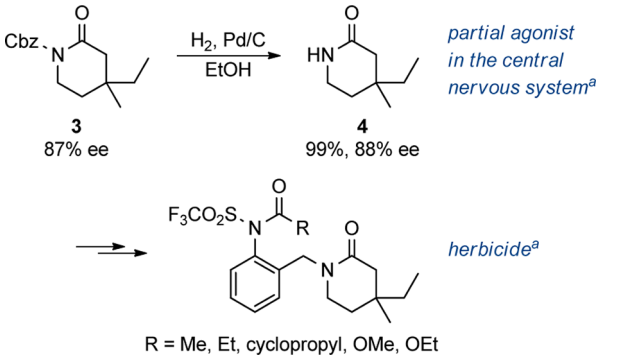
entry	L	Cu salt[b]	temp (°C)	yield[c] (%)	ee[d] (%)
1	**L1**	CuNp	−10	33	64 (+)
2	**L2**	CuTC	−10	58	78 (−)
3	**L2**	**CuTC**	**−30**	**53**	**87 (−)**

[a] Reactions performed on a 0.2 mmol scale, under an Ar atmosphere. Conversion = 100%, determined by ^{1}H NMR or TLC. [b] CuNp = solution of copper(II) naphthenate in pentane; CuTC = Cu(II) thiophene-2-carboxylate. [c] Isolated yields. [d] Determined by SFC on a chiral stationary phase.

known 4-methyl-5,6-dihydropyridin-2(1*H*)-one.[17] By applying the optimized reaction conditions in the presence of triethylaluminum, we were pleased to obtain the desired product **3** in 33% of isolated yield and a promising enantiomeric excess of 64% (Table 4, entry 1). Then, a nice improvement could be achieved by the use of the CuTC/**L2** complex (entry 2). By lowering the reaction temperature to −30 °C, the product **3** could be formed in practical yield (53%) and good optical purity (87% ee) (entry 3).

It should be noted that lactam **3** could serve as a precursor for the preparation of compounds with interesting properties (Scheme 1). Its deprotection by hydrogenation was carried out to form the product **4**, of which the racemic form showed biological activities (partial agonist in the central nervous system).[18] The lactam **4** could also be considered as an intermediate in the synthesis of a family of herbicides, whose general strucure is depicted in Scheme 1.[19]

Scheme 1. Synthetic Utility of Lactam **3**



[a] Properties observed for the racemic form of the corresponding compounds.

In conclusion, a series of alkenyl groups have been successfully introduced to an α,β-unsaturated lactam, affording valuable building blocks in the synthesis of enantioenriched nitrogen-containing heterocycles. The chiral SimplePhos/copper complex proved to also be highly efficient to promote the 1,4-addition of trialkylaluminum reagents. β-Methyl-substituted δ-lactams were formed in very high optical purity. By slightly modifying the general procedure, the first example of ACA to β-substituted conjugated lactams is reported, allowing the formation of an all-carbon quaternary stereogenic center. Extension of this methodology is ongoing in our laboratory.

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Supporting Information Available. Experimental procedures, NMR spectra, and chiral separations for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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