# Synthesis of α,β-unsaturated γ-lactams *via* asymmetric iridium-catalysed allylic substitution

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**Syntheses of α,β-unsaturated γ-lactams are described that are based on ring-closing metathesis in combination with enantioselective Ir-catalysed allylic amination using *N*-Boc-*N*-(but-2-enoyl)-amine as a pronucleophile. As an example application, the synthesis of a Baclofen analogue is presented.**

δ-Substituted α,β-unsaturated γ-lactams are found among natural products, examples are the microcolins (**A**),[1] and they are useful as building blocks for the synthesis of a variety of biologically active compounds (Fig. 1). Due to their conformational rigidity, reactions at the double bond, notably cycloadditions and conjugate additions, proceed with a high degree of stereocontrol.[2,3c] For example, Barrett *et al.*[4] used the lactam **C** as an intermediate in the course of a total synthesis of the antifungal agent (−)-pramanicine (**B**). The 3-OH group was introduced by conjugate addition of a silylzincate, which proceeded with perfect *anti*-diastereoselectivity in quantitative yield, followed by a Tamao–Fleming oxidation. γ-Lactams have also been used as intermediates in syntheses of GABA derivatives,[5] for example, Baclofen analogues of type **D**, which are available from lactams **E** by conjugate addition of organocopper compounds and hydrolytic ring-opening.[6]

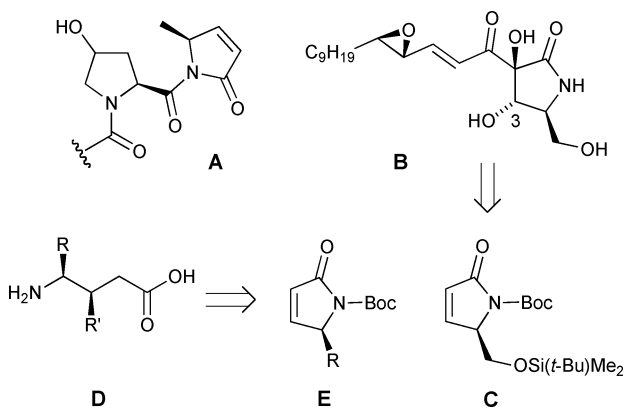
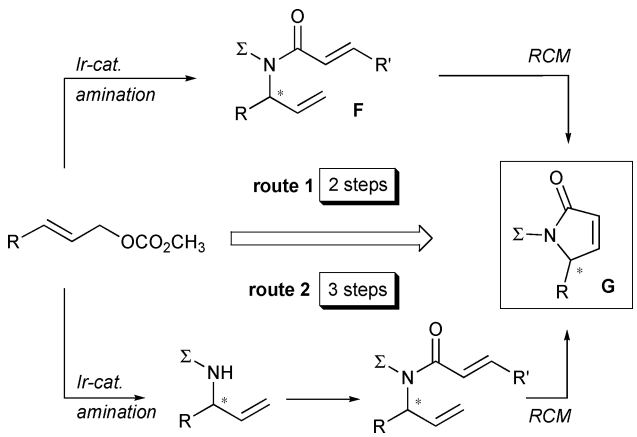



**Fig. 1** Biologically active γ-aminobutyric acid derivatives.

Non-racemic α,β-unsaturated γ-lactams[7] are usually prepared from α-amino acids,[3] for example, **C** and related compounds are derived from glutamic acid. Other approaches have only rarely been used.[2a,8] Herein, we describe a new route, which is based on the combination of an iridium-catalysed enantioselective allylic substitution[9] and a ring-closing metathesis (RCM). Two strategies, route 1 and route 2 (Scheme 1), were envisaged. Route 2 begins with the formation of a chiral allylamine, which is acylated with an acrylic acid derivative to give a diene that can serve as the starting material for ring-closing metathesis. Using allylamines prepared by methods other than an allylic substitution, Blechert and coworkers[10] successfully probed the metathesis part of this route with non-protected and *N*-benzyl-protected compounds **F**, *i. e.* Σ = H or Bn, R′ = H.




**Scheme 1** Concepts for the synthesis of γ-lactams.

Following this lead, we first investigated route 2. Realisation was straightforward because benzylamine has often been used as an *N*-nucleophile in iridium-catalysed aminations.[11,12] However, deprotection of *N*-benzyl derivatives with methods other than catalytic hydrogenation is very problematic. Therefore, we were interested in probing further protecting groups. On the basis of our recent implementation of *N*,*N*-diacylamines as ammonia equivalents in Ir-catalysed allylic substitution[13] we envisaged the shorter route 1 (Scheme 1), which is based on the pronucleophile **2** (Scheme 2).[14] Route 1 would enable the preparation of Boc-protected amides **3** in a single step. Apart from its convenient removal, the *N*-Boc group is advantageous as it activates addition reactions at the double bond of the γ-lactams.

Ir-catalysed allylic substitutions were run using conditions previously described[13] (*cf.* General Procedure†). With the help of ligands **L1** and **L2** (Scheme 2), regioselectivity of up to 98 : 2 in favour of the branched product and enantiomeric excesses of up to >99% ee were achieved.

The scope of the substitution reaction was examined with a variety of carbonates, containing alkyl, aryl, and functionalised alkyl substituents. The results are displayed in Table 1. Depending on the group R of the carbonate **1**, either the use of amide **2** (conditions A, "salt-free") or its sodium salt (conditions B) led to

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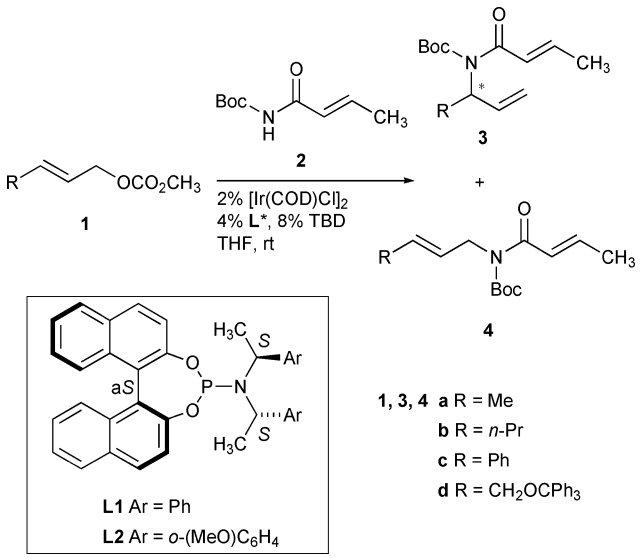
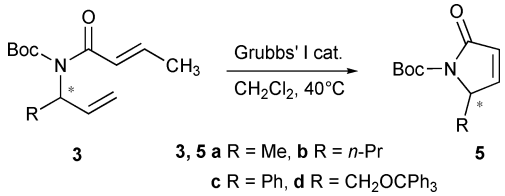
**Table 1** Ir-catalysed allylic substitutions according to Scheme 2 (*cf.* also the General Procedure†)

| Entry | Substrate | Conditions[a] | Ligand | Time/h | Yield (%)[b] | **3** : **4** | ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | A | *ent*-**L2** | 0.7 | 74 | 98 : 2 | >98 (−)-(*S*) |
| 2 | **1a** | A | **L1** | 48 | 54[d] | 98 : 2 | 94 (+)-(*R*) |
| 3 | **1a** | B | **L1** | 2.5 | 73[e] | 95 : 5 | n. d. |
| 4 | **1a** | B | **L2** | 4 | 71[e] | 93 : 7 | n. d. |
| 5 | **1b** | A[f] | *ent*-**L2** | 2 | 78 | 98 : 2 | 99[g] |
| 6 | **1b** | B[f] | *ent*-**L2** | 1.5 | 76 | 97 : 3 | 98[g] |
| 7 | **1c** | A[f] | *ent*-**L2** | 24 | 64 | 98 : 2 | 95 (+) |
| 8 | **1c** | B | *ent*-**L2** | 3 | 79 | 98 : 2 | >98 (+) |
| 9 | **1d** | A[f] | **L2** | 4 | 77 | 96 : 4 | >99 (+) |
| 10 | **1d** | B[f] | *ent*-**L2** | 1.5 | 90 | 91 : 9 | 98 (−) |
| 11 | **1d** | A[f,h] | **L2** | 1 | 76 | 93 : 7 | >99 (+) |

[a] If not stated otherwise, reactions were carried out on a 0.5 mmol scale of **1** using 2 mol% of $[Ir(COD)Cl]_2$, 4 mol% of ligand and 2 h of activation with TBD (8 mol%); A: pronucleophile **2** (0.6 mmol) was used neat; B: the sodium salt of **2** (0.6 mmol), generated by addition of 0.6 mmol of NaH in 0.5 mL THF followed by removal of the solvent, was used neat. [b] Yield of the combined isolated products **3** and **4**. [c] Determined by HPLC on chiral columns ($CHCl_3$, 578 nm).[18] In brackets: sign of the optical rotation of **3**. In the case of **1a**, the absolute configuration was verified by synthesis of (*S*,*S*)-**8**. [d] Incomplete conversion; the reaction was carried out on a 10 mmol scale with only 1 mol% of $[Ir(COD)Cl]_2$, 2 mol% of ligand and 4 mol% of TBD. [e] Yield including 20% isomerised product. [f] 5–30 min of activation with TBD (8 mol%).[17] [g] Optical rotation close to 0 at 578 nm. [h] Reaction at 45 °C.




**Scheme 2** Ir-catalysed allylic substitutions with the pronucleophile **2**.[16]




**Scheme 3** Ring-closing metathesis to give α,β-unsaturated γ-lactams.

**Table 2** Ring-closing metathesis according to Scheme 3

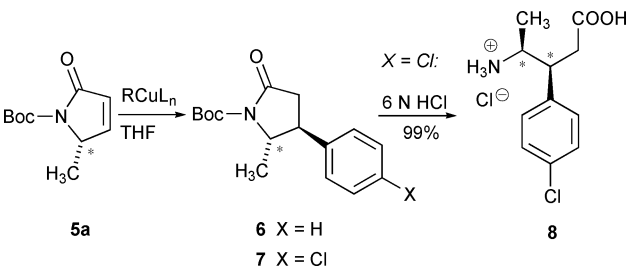
| Entry | Substrate | Mol% of catalyst | Time/h | Yield (%) |
|---|---|---|---|---|
| 1 | **3a** | 2.5 | 8[a] | 82–92 |
| 2 | **3b** | 5 | 9 | 81 |
| 3 | **3c** | 5 | 6 | 80 |
| 4 | **3d** | 5 | 5[a] | 77–81 |

[a] Reaction at 45 °C followed by 1 d at rt.

better results.[15] In the case of R = Me (entries 1–4) results using salt-free conditions A were superior, because under conditions B the product **3a** contained *ca.* 20–30% of a tautomer as side product. With **1b** and **1c** better results were obtained with conditions B (entries 4–8), while in the case of the carbonate **1d** the salt-free conditions gave vastly superior results (entries 9–11). Note that an increase of the reaction temperature led to a faster reaction with almost identical selectivities (entry 11).

Ring-closing metathesis, using 2.5–5 mol% of Grubbs' catalyst I in dichloromethane under reflux, proceeded with high yield (Scheme 3, Table 2). Enantiomeric excess of the products was determined in order to detect racemisation in the RCM step. No racemisation was found.[19] Furthermore, partial isomerisation of the double bond was not found in the case of the *N*-Boc-protected compounds.[20] Note that lactam **5d** is a an equivalent of compound **C** (Fig. 1), *i. e.* a potentially useful chiral building block.

Next, conjugate additions of organocopper compounds were studied, in order to prepare disubstituted lactams, which upon hydrolysis would yield GABA analouges with potentially interesting biologic activity. The addition of *alkyl*copper reagents to **5a** was reported by Belliotti *et al.*[6] We now disclose our results on the reaction of **5a** with *aryl*copper reagents (Scheme 4).




**Scheme 4** Conjugate addition of organocopper compounds.

**Table 3** Conjugate additions according to Scheme 4

| | Copper reagent | | | |
|---|---|---|---|---|
| Entry | Precursor | Copper salt | T/°C | Yield[a](%) |
| 1 | PhMgCl (2 equiv.) | CuBr (1 equiv.) | −40[b] | 50 |
| 2 | PhLi (6 equiv.) | CuI (3 equiv.), TMSCl | −75→10[c] | 90 |
| 3 | 4-Cl-($C_6H_4$)-MgCl (2 equiv.) | CuBr (1 equiv.) | −75[b] | (60)[d] |
| 4 | 4-Cl-($C_6H_4$)Li (6 equiv.) | CuI (3 equiv.), TMSCl | −75→10[c] | 84 |

[a] Yield of pure **6** or **7**. [b] Generation of the cuprate at −10 °C. [c] Generation of the cuprate at −30 °C. [d] 1 : 1 Mixture of *cis*- and *trans*-**7**.

First following Belliotti *et al.*, additions of Normant cuprates to the lactam **5a** were tried, but yields of 30–50% were not satisfactory (Table 3, entries 1 and 3). In the case of a copper reagent derived from 4-chlorophenylmagnesium chloride diastereoselectivity was also low. Distinctly better results were achieved with Gilman cuprates (entries 2 and 4) in combination with $Me_3SiCl$.

Reaction products with the *trans*-configuration were preferentially formed, as previously found for similar conjugate additions to lactams.[21] The product **7** from the reaction according to entry 4 of Table 3 was treated with 6 N HCl[22] under reflux to effect cleavage of the Boc-protecting group and ring-opening to yield the Baclofen derivative **8**, which is a potential monoamine oxidase inhibitor.[5] The relative and absolute configuration of this compound was established by X-ray crystal structure analysis.[23]

In conclusion, an enantioselective synthesis of α,β-unsaturated γ-lactams based on Ir-catalysed allylic substitution starting from achiral materials has been developed. A key element is the pronucleophile **2**, which allows us to carry out an allylic substitution reaction and subsequent RCM to give the target compounds with >98% ee in up to 67% yield over two steps. The Baclofen derivative **8** was prepared *via* addition of a Gilman cuprate to lactam **5a**. The lactam **5d** is a chiral building block equivalent to lactam **C**.

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## Notes and references

† General procedure: Success with the following procedure requires dry THF (<35 μg $mL^{-1}$ of $H_2O$, Karl Fischer titration). Under argon, a solution of $[Ir(COD)Cl]_2$ (0.02 mmol) and **L*** (0.04 mmol) in dry THF (1 mL) was treated with TBD[16] (0.08 mmol). After stirring for 5 min–2 h[17] at rt the allylic carbonate (0.50 mmol) was added, and the mixture was stirred for 5 min at rt. Then the pronucleophile **2** (0.60 mmol) or its sodium salt (0.60 mmol), prepared by reaction with NaH (0.60 mmol) in THF (0.5 mL), was added neat and the mixture was stirred until thin layer chromatography (TLC) indicated complete conversion. The solvent was removed under reduced pressure, and the residue was analysed with respect to the content of branched and linear product by $^1$H NMR and/or by isolation of both products by flash chromatography on silica.[15]

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12 Additionally, benzhydrylamine and *p*-methoxybenzylamine were used as nucleophiles to give allylamines with excellent enantio- and regioselectivities. The allyamines were transformed into *N*-(3-methylacryloyl)-amines **F**, which were subjected to RCM to furnish lactams **G**; S. Spiess, MSc thesis, Universität Heidelberg, 2006; C. Berthold, MSc thesis, Universität Heidelberg, 2006.
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15 Diacylamides **3** are somewhat sensitive to acidic conditions. In particular, lengthy chromatographic processes using silica cause lowering of yield.
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18 HPLC Data for **3** (Table 1), Daicel columns, 250 × 4.6 mm, 5 μm with guard cartridge, 10 × 4 mm, 0.5 mL $min^{-1}$; **3a**: Chiralcel OD-H, *n*-hexane/*i*-PrOH 99.9 : 0.1, rt, 220 nm, $t_R$[(−)-(*S*)-**3a**] = 19 min, $t_R$[(+)-(*R*)-**3a**] = 21 min; **3b**: Chiralcel OD-H, *n*-hexane/*i*-PrOH 99.9 : 0.1, rt, 220 nm, $t_R$[**3b**] = 16 min and 19 min; **3c**: Chiralcel AD-H, *n*-hexane/*i*-PrOH 98 : 2, rt, 220 nm, $t_R$[(+)-**3c**] = 10 min, $t_R$[(−)-**3c**] = 11 min; **3d**: Chiralcel OD-H, *n*-hexane/*i*-PrOH 99 : 1, rt, 210 nm, $t_R$[(+)-**3d**] = 11 min, $t_R$[(−)-**3d**] = 18 min.
19 An exception is the compound **5**, R = 2-furyl, which was formed with complete racemisation.
20 Several related amides **F** (R′ = $CH_3$ and Σ = Bn or *p*-$MeOC_6H_4$) were also subjected to RCM. Double bond isomerisation was only found in the case R = *n*-Pr, likely caused by residual Ru compounds in the products, *cf.* (*a*) M. B. Dinger and J. C. Mol, *Organometallics*, 2003,

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22 T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119, and references cited therein.
23 Crystal data for **8**: $C_{11}H_{15}Cl_2NO_2$, $M = 264.14$, monoclinic, space group $P2_1$, $a = 7.3431(3)$, $b = 6.1580(3)$, $c = 14.2504(6)$ Å, $\alpha = 90.0$, $\beta = 90.828(1)$, $\gamma = 90.0°$, $V = 644.32(5)$ Å$^3$, $T = 200$ K, $Z = 2$, $\mu = 0.489$ mm$^{-1}$,6344 reflections measured, 2881 unique ($R_{int} = 0.0539$), 2286 observed [$I > 2\sigma(I)$], $R_1 = 0.046$, $wR_2 = 0.087$ [$I > 2\sigma(I)$], Flack −0.08(7), CCDC reference numbers 644739. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b708571k.

 