An Asymmetric Domino Three-Component Synthesis of β-Lactams

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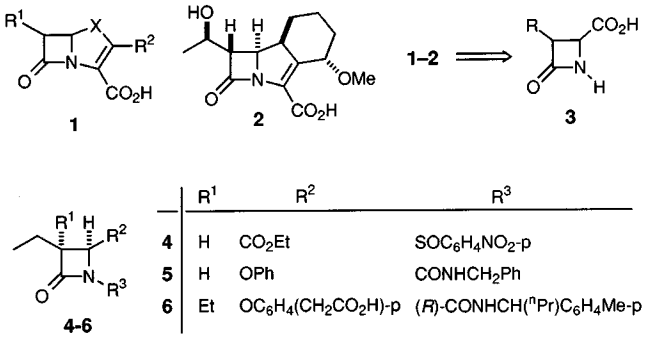
Lithium dialkylcuprates react either in a sequential one-pot or in a domino "three-component" fashion with chiral Michael acceptors, like Oppolzer's *N*-enoyl-2,10-camphorsultams **7** and **11** or Evans' *N*-enoyl-4-phenyl-1,3-oxazolidin-2-ones **8** and **13**, and *N*-(methoxycarbonylmethylidene)(4-methoxyphenyl)amine **9** to afford the corresponding *cis*-3-alkyl-4-methoxycarbonyl-1-(4-methoxyphenyl)azetidin-2-ones **10**, **14–15** in overall yields of 40–67% and enantiomeric excesses of 91–99 %.

Introduction

The development of new approaches to the stereocontrolled synthesis of β-lactams continues to be of crucial importance within the context of the most widely employed class of antimicrobial agents, the β-lactam antibiotics.[1] The majority of these compounds are characterized by a bicyclic structural framework of type **1**. Amongst them, the trinems of Glaxo Wellcome laboratories, particularly the methoxy derivative **2**, which is under phase-II clinical trial, exemplify the degree of evolution of this area.[2][3] As a consequence of this current interest, several strategies for the construction of bicyclic β-lactam antibiotics have been developed and the topic has been widely documented and reviewed several times.[4] The most commonly used strategy to access these systems lies in the prior construction of a monocyclic non-racemic β-lactam such as **3**, followed by chemical manipulations at N-1 and C-4 positions of the azetidinone nucleus and ring closure at a later stage of the synthesis. Besides this significance, 3-alkyl-4-alkoxycarbonylazetidin-2-ones **4**−**6** have also been found to be important inhibitors of the human leukocyte elastase (HLE), which is believed to be at the origin of the enzymolytic degradation of a variety of proteins, including the structural proteins, fibronectin, collagen, and elastin.[5] Therefore, the high number of methods currently available for the stereoselective preparation of monocyclic β-lactams is not surprising.[6] With few exceptions, the majority of these methods involve a combination of two reactants that provide the required β-lactam framework in a single step. Special attention has been put on the use of the metal ester enolate−imine condensation because of the easy availability of the starting materials and the high levels of asymmetric induction often attained through the use of either chiral carboxylic acid esters or chiral imines.[7]

Figure 1. Representative families of β-lactam antibiotics and elastase inhibitors characterized by the presence of aliphatic chains at the C-α position of the β-lactam carbonyl group; for the nature of R^1, X and R^2 substituents and configurations in **1**, see ref.[1]



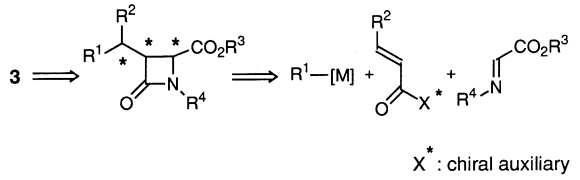
	R^1	R^2	R^3
4	H	CO_2Et	$SOC_6H_4NO_2$-p
5	H	OPh	$CONHCH_2Ph$
6	Et	$OC_6H_4(CH_2CO_2H)$-p	(*R*)-$CONHCH(^nPr)C_6H_4Me$-p

We wish to report here a conceptually different but in practice equivalent strategy of accessing β-lactams based on a ternary combination of components, namely, the conjugate addition of carbon nucleophiles, i.e. organocuprate reagents, to α,β-unsaturated carboxylic acid derivatives and subsequent condensation of the resulting enolates with an imine. This strategy (Figure 2), distinguished by the disconnection of two carbon−carbon bonds, involves an efficient combination of three reactants either in a sequential or in a one-pot domino process. As a result, several parameters must be carefully controlled, vide infra, and particularly the reactivity of the in situ generated copper enolates which have essentially been ignored within the context of β-lactam synthesis.[7][8]

[+] X-ray crystal structure analysis.

  1434−193X/98/1010−2201 $ 17.50+.50/0

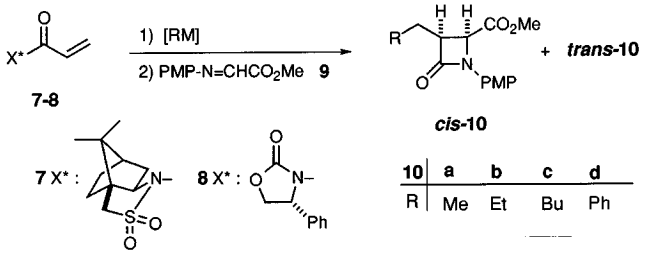
Figure 2. The three-component two-C−C bond forming approach to enantiomerically enriched 3-alkyl-4-alkoxycarbonylazetidin-2-ones



Results and Discussion

Prior to the present investigation, very few studies concerning the coupling reaction of three reactants to furnish β-lactams have been described. All of these cases have dealt with the addition of nitrogen nucleophiles to enoates followed by enolate trapping with an electrophile, thus involving only one carbon−carbon bond formation.[9] The resulting intermediate β-amino acids and/or esters, upon cyclization in a separate step, lead to the corresponding β-lactam product. In parallel to these studies, we have also reported on the addition of Fleming's higher order cyanosilylcuprate reagent to methyl crotonate followed by condensation with glyoxylate imines.[10] Therefore, our investigation was centered on the asymmetric conjugate addition of carbon nucleophiles to chiral α,β-unsaturated carbonyl systems and enolate trapping with glyoxylate imines.[11] The goal of this work was to establish the main chemical and stereochemical control elements that could govern the whole process outlined in Figure 2. The success of this proposal would be valuable for the development of an enantioselective version of the approach. To this end, the following issues had to be satisfactorily addressed: a) the selective attack of the organometallic nucleophile (i.e. the organocuprate reagent) at the β-carbon atom of the Michael acceptor versus the imine methine,[12] b) the sufficient reactivity of the enolate thus formed towards the imine, c) the achievement of the maximum stereoselectivity in the creation of the three possible new stereocenters, and d) the spontaneous cyclization of the intermediate β-amino ester anion to generate the expected β-lactam product.

Scheme 1. Three-component asymmetric synthesis of 3-alkyl-4-methoxycarbonylazetidin-2-ones from chiral acryloyl derivatives **7** and **8**



The structural variables studied to tune up the whole process were the chiral auxiliary (X*) of the Michael acceptor, the nature of the organocopper reagent and the substituents at the imine. The reaction, Scheme 1, was first checked according to a "sequential one-pot" procedure (consisting of a consecutive addition of the Michael acceptor and the imine to a solution of the cuprate reagent) using the *N*-enoylsultam **7** and the *N*-enoylamide **8** and some representative organocopper reagents.[13] For example, our first finding (see Table 1) was that Gilman reagents, by reaction with both **7** and **8** followed by one-pot enolate trapping with the imine **9**, produced *cis* β-lactam adducts **10a−d** in moderate diastereoselectivities[14] and high enantiomeric purities. On the other hand, cyanocuprates were less efficient, particularly in terms of *cis/trans* diastereoselectivity and chemical yield. Thus, in all but one case (entry 12), the *cis/trans* ratio were in the range 70:30 to 85:15. As shown in Table 1, the most striking feature of the method was the simultaneous improvement of the *cis/trans* diastereomeric ratio and the enantiomeric purity for the major isomer when the enolate trapping step was carried out at 0°C instead of at lower reaction temperatures (compare, for instance, entries 1/2,

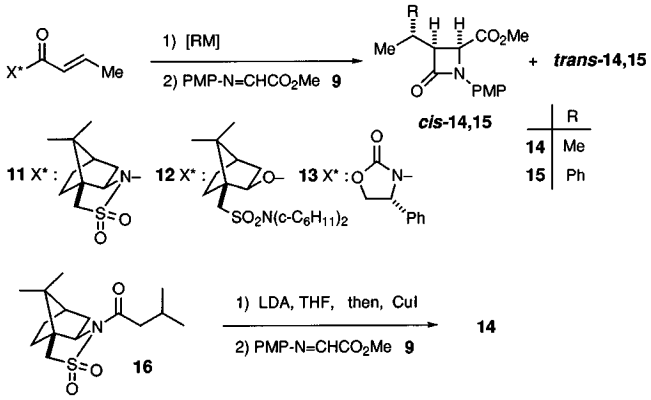
Table 1. Conjugate addition of cuprate reagents to acryloyl derivatives **7** and **8** followed by enolate trapping with glyoxylate imine **9**[a]

Entry	Michael acceptor	Cuprate	Imine trapping *T* [°C]/*t* [h]	Yield [%][b]	Product **10**	*d.r. cis/trans*[c]	*e.e.* [%][d]
1	**7**	Me_2CuLi	−78/14	55	**a**	60:40	94
2	**7**	Me_2CuLi	0/3	50	**a**	88:12	97
3	**7**	$Me_2CuCNLi_2$	0/3	30	**a**	70:30	94
4	**8**	$Me_2CuCNLi_2$	0/3	50	**a**	88:12	96
5	**7**	Et_2CuLi	−78/14	40	**b**	60:40	60
6	**7**	Et_2CuLi	0/3	60	**b**	70:30	88 (98)
7	**8**	Et_2CuLi	0/3	40	**b**	85:15	99
8	**8**	$Et_2CuCNLi_2$	0/3	25	**b**	75:25	96
9	**7**	Bu_2CuLi	−78/14	45	**c**	65:35	20
10	**7**	Bu_2CuLi	0/3	61	**c**	85:15	74
11	**8**	Bu_2CuLi	0/3	40	**c**	80:20	98
12	**8**	$Bu_2CuCNLi_2$	0/3	40	**c**	93:07	94 (98)
13	**8**	BuCuCNLi	0/3	10	**c**	85:15	—[e]
14	**7**	Ph_2CuLi	−78/14	50	**d**	55:45	97
15	**7**	Ph_2CuLi	0/3	54	**d**	75:25	98

[a] Reactions conducted on a $1\cdot10^{-3}$ mol scale of Michael acceptors. Molar ratio **7**,**8**/cuprate/imine = 1:1.1:1.5. − [b] Non-optimized yields of the isolated mixtures of *cis*- and *trans*-β-lactams. − [c] Diastereomers detected in the reaction crudes by 300-MHz ^{1}H NMR and confirmed by HPLC. − [d] Measured by HPLC (see Figure 3) for the *cis* isomers (3*S*,4*S*) (major) and (3*R*,4*R*) (minor). Values in brackets refer to the *e.e.* of crystallized products. − [e] Not determined.

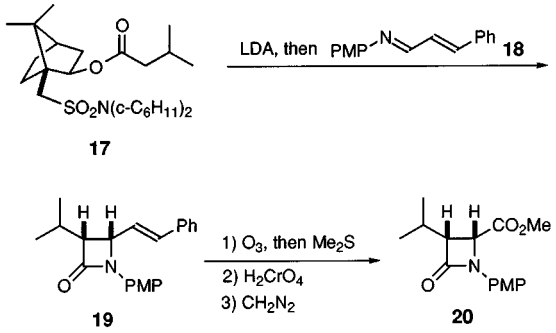
5/6, 9/10 and 14/15). In these instances, the *N*-enoylamide **8** was also better than the sulfonamide **7** to give essentially one *cis* enantiomer.

Scheme 2. Three-component asymmetric synthesis of 3-alkyl-4-methoxycarbonylazetidin-2-ones from chiral crotonoyl derivatives **11**, **12**, and **13**



Next, we examined the reaction of **11**, **12**, and **13**, Scheme 2, with methylcopper species and subsequent trapping with imine **9**. With the exception of **12** (entry 5, Table 2), the reaction sequence proceeded to give the expected β-lactam product **14** as major isomer. The best results were obtained with Gilman reagents and, once again, we found that in each case tested the enantiomeric purity of the resulting *cis*-β-lactam products increased notably when the enolate trapping was carried out at 0°C instead of at the usual low reaction temperature (−78°C) employed in the classical ester enolate−imine condensation. Differences in chemical behavior also arose when the enolates formed following our method were compared with metal enolates generated by deprotonation. For instance, Scheme 2, (1*S*,2*R*)-*N*-isovaleryl-2,10-camphorsultam (**16**) upon treatment with LDA in THF at −78°C for 1 h followed by the addition of 0.5 equiv. of copper(I) iodide or $CuBr \cdot SMe_2$ and imine **9**, gave β-lactam **14** in lower than 22% yield. Moreover, the product was obtained as a 65:35 (*cis/trans*) diastereomeric mixture showing an e.e. of 98% for the *cis*-(3*S*,4*S*) enantiomer. Without CuI, no β-lactam was formed at all.[15] The potential of this three-component coupling approach to β-lactams can also be illustrated by the handy preparation of the β-lactam **15** bearing three contiguous stereogenic centers. The first step was carried out according to the procedure of Hruby et al.[14c][14d] and the resulting enolate was treated with the imine **9** to give an oily product which, after purification by column chromatography, led to **15** along with its *trans* diastereomer in a ratio of 92:8. Compound **15** was isolated by crystallization from ethanol in 45% yield and the enantiomeric purity checked by chiral HPLC analysis was higher than 99%.

Scheme 3. Determination of the configuration of the β-lactam **14** by chemical correlation



The *cis* relative disposition of the vicinal methine protons at C-3 and C-4 in each β-lactam was easily confirmed on the basis of their coupling constants ($^3J_{3,4} \approx 5.9$ Hz). The absolute configuration (3*S*,4*S*) for **14** was established by chemical correlation with the β-lactam **19**, prepared from **17** as previously described by Hart el al.[16] Thus (Scheme 3), after preparative HPLC separation of the major (3*R*,4*R*) isomer **19**, its consecutive treatment with ozone, Jones reagent and diazomethane, afforded the 3-isopropyl-4-methoxycarbonylazetidin-2-one **20** in 39% overall yield. A comparative HPLC analysis of **14** and **20** (Figure 3) with the racemic β-lactam, prepared according to our previously described method,[17] showed their enantiomeric relationship, and confirmed the (3*S*,4*S*) configuration for **14**, which was also extended to **10a−d**. Additionally, compound **15** was submitted to a single-crystal X-ray analysis (Figure 4), thus

Table 2. Synthesis of β-lactams **14** and **15** by sequential three-component reaction of chiral Michael acceptors **11**−**13** and glyoxylate imine **9** with different methylcaprate reagents[a]

Entry	Michael acceptor	Cuprate	Imine trapping *T* [°C]/*t* [h]	Yield [%][b]	*d.r. cis/trans*[d]	*e.e.* [%][e]
1	**11**	Me_2CuLi	−78/14	62	94:6	98
2	**11**	Me_2CuLi	0/3	57	98:2	> 99
3	**11**	$Me_2CuMgBr$	0/3	67[f]	87:13	92
4	**11**	$Me_2CuCNLi_2$	0/3	40	99:1	> 99
5	**12**	Me_2CuLi	—[g]	—	—	—
6	**13**	Me_2CuLi	0/3	54	99:1	98
7	**13**	$Me_2CuMgBr$	0/3	59	92:8	83
8	**13**	$Ph_2CuMgBr$	−78 to 20/16	62[f]	92:8	> 99

[a] Reactions conducted on a $1 \cdot 10^{-3}$ mol scale of Michael acceptors. Molar ratio **11**−**13**/cuprate/imine = 1:1.1:1.5. − [b] Imine-trapping temperature. − [c] Non-optimized yields of the isolated mixtures of *cis*- and *trans*-β-lactams. − [d] Diastereomers detected in the reaction crudes by 300-MHz ^{1}H NMR and confirmed by HPLC. − [e] e.e. values relative to the (3*S*,4*S*) (major) and (3*R*,4*R*) (minor) *cis* isomers. − [f] 3 equiv. of **9** were needed to complete the reaction. − [g] Several temperature conditions were tried with addition reaction failure.

Figure 3. Enantiomeric ratio determination by HPLC on chiral stationary phase for 3-alkyl-4-methoxycarbonylazetidin-2-ones **14** [a)] and **20** [b)] by comparison with the racemic mixture [c)]; chiral stationary phase: Chiralpak-AS 250 × 4.6 mm; eluant: 2-PrOH/hexanes, 50:50

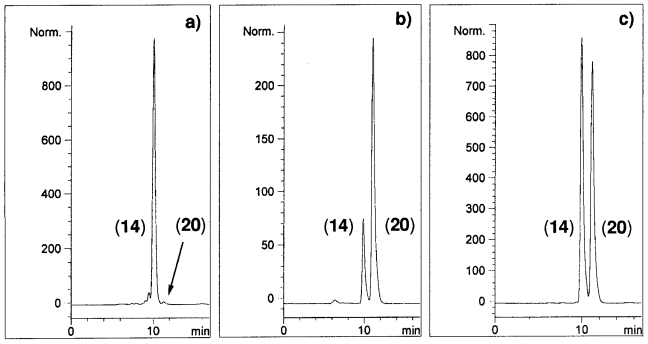
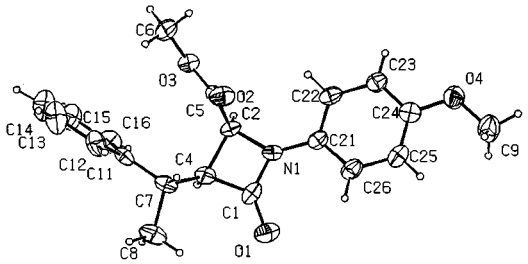


Figure 4. ORTEP representation of the X-ray structure of compound **15**; absolute configuration was checked using BIJVOET,[28] resulting in $B = 0.33(7)$ for the 53 strongest pairs, and $\chi = -1(2)$; both results are indications of the proposed configuration



confirming the stereochemical course of these reactions.[18]

The next question we addressed was to establish whether Gilman reagents would be able to kinetically differentiate the electrophilic centers of both starting materials (Michael acceptor and imine), with the aim to achieve the first domino-type entry to β-lactams.[19] To check out this possibility, a few experiments were carried out (see Table 3) involving the addition of several lithium dialkylcuprates to a precooled (0°C) mixture of Michael acceptors **7**, **8**, **11**, or **13** and imino ester **9** in THF as solvent. We obtained the expected β-lactam adducts **10** and **14** in similar diastereomeric and enantiomeric ratios than those attained using the sequential method.

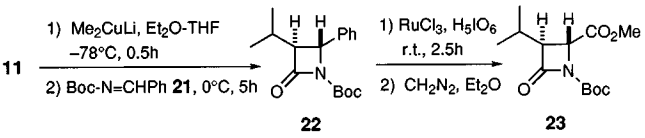
Finally, to establish the influence of the imine substituents on the reaction, we studied the behavior of two non-activated imines, *N*-benzylidene-(4-methoxyphenyl)amine and *N*-cinnamylidene-(4-methoxyphenyl)amine, towards Gilman cuprates and *N*-enoylcamphor-2,10-sultams **7** and **11**. Using both the sequential or the tandem method, the only carbon−carbon bond forming reaction was the conjugate addition and no enolate−imine reaction was observed. However, *N*-activated imines[20] such as *N*-Boc-imine **21** (see Scheme 4) showed a dramatically different behavior and smoothly gave the adduct **22** at 0°C in 62% yield as a single *trans* isomer according to the ^{1}H-NMR coupling constant ($^3J_{3,4}$ = 3.1 Hz) observed. The e.e. of **22** was > 99% and its absolute (3*S*,4*R*) configuration was established by circular dichroism analysis using Braun's method.[21] It

Table 3. Tandem conjugate addition of cuprate reagents to a mixture of chiral acryloyl derivatives **7** and **8** or crotonoyl derivatives **11**−**13** and glyoxylate imine **9**[a]

Entry	Michael acceptor	Cuprate	Yield [%][b]	*d.r.* *cis*/*trans*[c]	*e.e.* [%][d]
1	**7**	Me_2CuLi	40	85:15	98
2	**7**	Me_2CuLi	40	76:24	73
3	**7**	Bu_2CuLi	35	72:28	73
4	**11**	Me_2CuLi	55	97:3	> 99
5	**13**	Me_2CuLi	50	99:1	98

[a] Reactions conducted on a $1 \cdot 10^{-3}$ mol scale of Michael acceptors/cuprate/imine = 1:1.1:1.5. Addition of the cuprate reagent (1.1 mmol, 0.25 M in Et_2O) to a mixture of **7**, **11**, or **13** ($1 \cdot 10^{-3}$ mol) and **9** ($1.5 \cdot 10^{-3}$ mol) in THF (8.5 ml) at 0°C, followed by stirring at the same temperature for 3 h. − [b] Non-optimized yields of the isolated mixtures of *cis*- and *trans*-β-lactams. − [c] Diastereomers detected in the reaction crudes by 300-MHz ^{1}H NMR and confirmed by HPLC. − [d] e.e. values relative to the (3*S*,4*S*) (major) and (3*R*,4*R*) (minor) *cis* isomers.

Scheme 4. Three-component asymmetric synthesis of *trans* 3-alkyl-4-methocycarbonylazetidin-2-ones



is worth mentioning that the oxidative cleavage of the phenyl ring[22] in **22**, followed by methylation with diazomethane, provided **23**, thus extending the scope of the present method to the synthesis of both *cis*- and *trans*-α-alkyl-β-methoxycarbonyl-β-lactams in a highly convergent fashion.

Conclusion

Among the factors governing the activation-selectivity sequence involved in the tandem reaction of alkylcuprate reagents, chiral *N*-enoyl derivatives and imines to afford α-alkyl-β-lactams, it has been found that the following structural effects are of importance: a) the enolates generated by organollithium or organomagnesium cuprates are more reactive towards imines than those derived from the so-called higher order cyanocuprates, b) Oppolzer's *N*-enoylsultams and Evans' *N*-enoyloxazolidinones are of similar efficiency to induce both asymmetric conjugate addition and subsequent stereoselective enolate condensation with imines, and c) the carbonyl and amine components of the imine used play a fundamental role to activate its addition to the intermediate enolate and to control the stereochemical course of the reaction. Accordingly, while imines bearing electron-withdrawing *C*-substituents afford mainly *cis*-α-alkyl-β-lactams and the *cis/trans* ratio increases with the condensation reaction temperature, the imines with *N*-electron-withdrawing substituents lead to *trans*-α-alkyl-β-lactams at low temperature.

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Experimental Section

General Remarks: All reactions involving cuprates were carried out under dry N_2 using oven-dried glassware and syringes. THF was distilled from sodium and benzophenone (indicator). Organocuprate reagents were prepared using the following stoichiometries and conditions:[23] Me_2CuLi: from MeLi (1.6 M in Et_2O, 2 equiv.) and CuI (1 equiv.) in Et_2O at 0°C; Et_2CuLi: from EtLi (1.2 M in Et_2O, 2 equiv.) and CuI (1 equiv.) in Et_2O at −78°C; Bu_2CuLi: from BuLi (1.6 M in hexane, 2 equiv.) and CuI (1 equiv.) in Et_2O at −78°C; Ph_2CuLi: from PhLi (1.2 M in Et_2O, 2 equiv.) and CuI (1 equiv.) in Et_2O at −0°C; $Me_2CuCNLi_2$: from MeLi (1.6 M in Et_2O, 2 equiv.) and CuCN (1 equiv.) in THF at −78°C; $Et_2CuCNLi_2$: from EtLi (1.2 M in Et_2O, 2 equiv.) and CuCN (1 equiv.) in THF at −78°C; $Bu_2CuCNLi_2$: from BuLi (1.6 M in hexane, 2 equiv.) and CuCN (1 equiv.) in THF at −78°C; BuCuCNLi: from BuLi (1.6 M in hexane, 1 equiv.) and CuCN (1 equiv.) in Et_2O at −78°C; $Me_2CuMgBr$ or $Ph_2CuMgBr$: from MeMgBr or PhMgBr (3.0 M in Et_2O, 2 equiv.), $CuBr\cdot SMe_2$ (1 equiv.) and SMe_2 (17 equiv.) in THF at −40°C. The following compounds were prepared according to literature procedures: (1*S*,2*R*)-*N*-propenoyl-2,10-camphorsultam (**7**),[24] (4*R*)-4-phenyl-3-propenoyl-1,3-oxazolidin-2-one (**8**),[24] *N*-[(methoxycarbonyl)methylidene]-(4-methoxyphenyl)amine (**9**),[25] (1*S*,2*R*)-*N*-[(*E*)-2-butenoyl]-2,10-camphorsultam (**11**),[26] (1*S*,2*R*)-10-(*N*,*N*-dicyclohexylsulfamoyl)isoborneyl crotonate (**12**),[27] (4*R*)-3-[(*E*)-2-butenoyl-4-phenyl-1,3-oxazolidin-2-one (**13**),[14d] *N*-benzylidene-*tert*-butoxycarbonylamine (**21**)[20b]. − M.p.: Büchi SMP-20, uncorrected values. − IR: Shimadzu IR-435. − NMR: Varian VXR 300 (300 MHz and 75 MHz, for ^1H and ^{13}C, respectively). For ^1H NMR, $CDCl_3$ as solvent, $\delta_H = 7.26$; for ^{13}C NMR, $CDCl_3$ as solvent, $\delta_C = 77.0$. − MS: Finnigan MAT GCQ (70eV), ion-trap, GC-MS coupling (column: fused silica, 15 m, 0.25 mm, phase SPB-5). − Optical rotations: Perkin-Elmer 243 B polarimeter. CH_2Cl_2 as solvent at 25 ± 0.2°C. − HPLC: Hewlett-Packard 1050, (DAD detector, λ = 254 nm). Enantiomeric excesses of β-lactams **10a**−**d** and **14** were determined using chiral stationary-phase columns, upon comparison with the racemic standards.[17] Analysis conditions for **10a**, **10d**, **14**, **20**, and **23**: Chiralpak-AS 250 × 4.6 mm column; eluant: 2-PrOH/hexane from 50:50 to 30:70. Analysis conditions for **11b**−**c**: Chiracel-OD 250 × 4.6 mm column; eluant: 2-PrOH/hexane, 20:80. Flow rates of 0.5 ml/min were used in all cases. Flash chromatography was performed on silica gel plates (Merck Kiesegel-60, 230−400 mesh) using mixtures of EtOAc and hexane as eluants.

General Procedure for the Preparation of α-Alkyl-β-lactams **11** *and* **14**: Methyllithium (1.38 ml, 1.6 M, $2.2\cdot10^{-3}$ mol) was added dropwise to a suspension of CuI (0.21 g, $1.1\cdot10^{-3}$ mol) in Et_2O (4.4 ml) kept under nitrogen at 0°C, and the mixture was stirred for 30 min at the same temperature. Once the mixture was cooled at −78°C, a solution of the corresponding Michael acceptor **7**−**8** or **11**−**13** ($1.0\cdot10^{-3}$ mol) in THF (4 ml) was added dropwise and the mixture stirred at the same temperature. Then, a solution of **9** (0.29 g, $1.5\cdot10^{-3}$ mol) in THF (4 ml) was added and the mixture was stirred at 0°C for 3 h. After this time, the reaction mixture was diluted in CH_2Cl_2 (30 ml) and washed with sat. NH_4Cl (3 × 30 ml). The organic layer was dried with $MgSO_4$, the solvents were evaporated, and the resulting product was treated with Amberlyst-15(Dry)® ion-exchange resin (5 g) in CH_2Cl_2 for 2 h, filtered and purified by column chromatography (230−400 mesh silica gel; eluant: EtOAc/hexane, 1:14).

10a: 0.13 g (50%) of a 88:12 mixture of *cis* and *trans* isomers. Crystallization from cyclohexane gave *cis*-**10a**, white solid, m.p. 102−104°C. − $[\alpha]_D^{25} = -136.3$ (c = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 1732 cm^{-1} (C=O). − ^1H NMR ($CDCl_3$): δ = 1.11 (t, J = 6.8 Hz, 3 H, CH_2CH_3), 1.560−1.98 [m, 2 H, CH_2CH_3), 3.54 (dt, J = 6.0, 8.0 Hz, 1 H, $CHCH_2CH_3$), 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.63 (d, J = 6.0 Hz, 1 H, $CHCO_2CH_3$) 6.89 (d, J = 9.0 Hz, 2 H, aromatic H), 7.26 (d, J = 9.0 Hz, 2 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 11.8, 19.0, 52.4, 54.7, 55.3, 55.5, 114.4, 117.8, 131.0, 156.2, 165.6, 169.5. − MS (70 eV) *m/z* (%): 263 (16.3), 149 (44.6), 134 (100.0). − $C_{14}H_{17}NO_4$ (263.3): calcd. C 63.87, H 6.51, N 5.32; found C 63.50, H 6.60, N 5.23.

10b: 0.09 g (40%) of a 85:15 mixture of *cis* and *trans* isomers. Crystallization from cyclohexane gave *cis*-**10b**, white solid, m.p. 84−86°C. − $[\alpha]_D^{25} = -148.7$ (c = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 1748 cm^{-1} (C=O), 1734 (C=O). − ^1H NMR ($CDCl_3$): 0.96 (t, J = 6.8 Hz, 3 H, CH_2CH_3), 1.42−1.80 (m, 4 H, $CH_2CH_2CH_3$), 3.58 (dt, J = 6.0, 7.4 Hz, 1 H, $CHCH_2CH_2CH_2$), 3.79 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.60 (d, J = 6.0 Hz, 1 H, $CHCO_2CH_3$), 6.86 (d, J = 9.0 Hz, 2 H, aromatic H), 7.24 (d, 2 H, J = 9.0 Hz, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 13.9, 20.6, 27.5, 52.4, 53.0, 53.4, 55.4, 55.5, 114.4, 117.8, 131.0, 156.2, 165.8, 169.6. − MS (70 eV) *m/z* (%): 277 (8.4), 149 (34.8), 134 (100.0). − $C_{15}H_{19}NO_4$ (227.3): calcd. C 64.97, H 6.91, N 5.05; found C 65.07, H 6.60, N 5.13.

10c: 0.12 g (40%) of a 80:20 mixture of *cis* and *trans* isomers. Crystallization from cyclohexane gave *cis*-**10c**, white solid, m.p. 50−52°C. − $[\alpha]_D^{25} = -110.9$ (c = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 1738 cm^{-1} (C=O), 1728 (C=O). − ^1H NMR ($CDCl_3$): 0.88 (t, J = 6.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.24−1.77 [m, 8 H, $(CH_2)_2CH_3$], 3.55 [dd, J = 6.0, 7.9 Hz, 1 H, $CH(CH_2)_4CH_3$], 3.76 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.58 (d, J = 6.0 Hz, 1 H, $CHCO_2CH_3$), 6.84 (d, J = 9.0 Hz, 2 H, aromatic H), 7.21 (d, J = 9.0 Hz, 2 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 13.9, 22.3, 25.4, 26.9, 31.6, 52.3, 53.1, 55.3, 55.4, 114.3, 117.7, 130.9, 156.2, 165.7, 169.5. − MS (70 eV) *m/z* (%): 305 (7.2), 149 (39.1), 134 (100.0). − $C_{17}H_{23}NO_4$ (305.4): calcd. C 66.86, H 7.59, N 4.59; found C 66.67, H 7.60, N 4.83.

10d: 0.16 g (40%) of a 97:3 mixture of *cis* and *trans* isomers. Crystallization from cyclohexane gave *cis*-**10d**, white solid, m.p. 112−114°C. − $[\alpha]_D^{25} = -63.3$ (c = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 1736 cm^{-1} (C=O), 1727 (C=O). − ^1H NMR ($CDCl_3$):δ = 2.96 (dd, J = 9.3, 15,0 Hz, 1 H, *H*CHPh), 3.25 (dd, J = 6.8, 15,0 Hz, 1 H, *H*CHPh), 3.65 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.96 [dt, J = 6.6, 9.2 Hz, 1 H, $CHCH_2Ph$), 4.60 (d, 1 H, J = 6.0 Hz, $CHCO_2CH_3$), 6.86 (d, J = 9.0 Hz, 2 H, aromatic H), 7.22−7.34 (m, 7 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 30.8, 52.2, 53.4, 54.9, 55.2, 114.2, 117.6, 126.5, 128.4, 128.7, 130.7, 137.2, 156.2, 164.7, 169.1. − MS (70 eV) *m/z* (%): 325 (22.7), 149 (59.3), 134 (100.0). − $C_{15}H_{19}NO_4$ (325.4): calcd. C 70.14, H 5.89, N 4.30; found C 69.90, H 6.01, N 4.33.

14: 0.16 g (57%) of a 97:3 mixture of *cis* and *trans* isomers. Crystallization from cyclohexane gave *cis*-**14**, white solid, m.p. 143−145°C. − $[\alpha]_D^{25} = -108.7$ (c = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 1741 cm^{-1} (C=O), 1728 (C=O). − ^1H NMR ($CDCl_3$): δ = 0.96 [d, J = 6.8 Hz, 3 H, $CH(CH_3)_2$], 1.20 [d, J = 6.8 Hz, 3 H, $CH(CH_3)_2$], 2.07−2.15 [m, 1 H, $CH(CH_3)_2$], 3.28 [dd, J = 3.1, 9.1 Hz, 1 H, $CHCH(CH_3)_2$] (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.58 (d, J = 6.0 Hz, 1 H, $CHCOOCH_3$), 6.86 (d, J = 9.0 Hz, 2 H, aromatic H), 7.22 (d, J = 9.0 Hz, 2 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 20.3, 21.3, 26.1, 52.3, 55.1, 55.3, 60.4, 114.2, 127.5, 130.8, 156.1, 165.0, 169.7. − MS (70 eV) *m/z* (%): 277 (22.8), 149

(47.9), 134 (100.0). − $C_{15}H_{19}NO_4$ (277.3): calcd. C 64.97, H 6.91, N 5.05; found C 64.80, H 6.90, N 5.15.

Preparation of **15**: Phenylmagnesium bromide (2.0 ml, 3 M, $6.0\cdot10^{-3}$ mol) was added dropwise to a solution of $CuBr\cdot SMe_2$, (0.62 g, $3.0\cdot10^{-3}$ mol) and SMe_2 (3.6 ml) in THF (7.0 ml) kept under nitrogen at −40°C, and the mixture was stirred for 10 min at the same temperature and warmed to −10°C. A solution of (4*R*)-3-[(*E*)-2-butenoyl]-4-phenyl-1,3-oxazolidin-2-one (**13**) (0.46 g, $2.0\cdot10^{-3}$ mol) in THF (4 ml) was added dropwise during 1 h and the mixture was stirred at the same temperature for 10 min. Once the mixture was cooled to −78°C, a solution of **5** (1.16 g, $6.0\cdot10^{-3}$ mol) in THF (4 ml) was added and the mixture was stirred from −78°C to room temperature during 16 h. After this time, the reaction mixture was diluted in CH_2Cl_2 (30 ml), washed with sat. NH_4Cl (3 × 30 ml), the organic layer was dried with $MgSO_4$, the solvents were evaporated, and the resulting reaction product was treated with Amberlyst-15(Dry)® ion-exchange resin (5 g) in CH_2Cl_2 for 2 h, filtered, and purified by column chromatography (230−400 mesh silica gel; eluant: EtOAc/hexanes, 1:4) to afford **15**, 0.31 g (45%) as 92:8 mixture of *cis* and *trans* isomers. Crystallization from cyclohexane gave *cis*-**16**, white solid, m.p. 162−164°C. − $[\alpha]_D^{25}$ = +99.7 (*c* = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 1748 cm^{-1} (C=O), 1736 (C=O). − ^1H NMR ($CDCl_3$): δ = 1.50 [d, *J* = 6.9 Hz, 3 H, CH(Ph)C*H*$_3$], 3.30 (s, 3 H, OCH_3), 3.36 [q, *J* = 6.9 Hz, 1 H, C*H*(Ph)CH_3], 3.77 (s, 3 H, OCH_3), 3.92 [dd, *J* = 5.8, 11.9 Hz, 1 H, C*H*CH(Ph)CH_3], 4.45 (d, *J* = 5.7 Hz, 1 H, C*H*CO_2CH_3), 6.85 (d, *J* = 9.0 Hz, 2 H, aromatic H), 7.13−7.37 (m, 7 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 22.6, 37.3, 52.1, 54.8, 55.5, 57.9, 114.4, 117.7, 126.8, 128.6, 130.8, 143.6, 156.3, 165.0, 169.1. − MS (70 eV) *m/z* (%): 339 (6.8), 149 (21.3), 134 (100.0). − $C_{20}H_{21}NO_4$ (339.4): calcd. C 70.78, H 6.24, N 4.13; found C 70.62, H 6.45, N 4.24.

Procedure for the Preparation of **22**: Methyllithium (1.38 ml, 1.6 M, $2.2\cdot10^{-3}$ mol) was added dropwise to a suspension of CuI (0.21 g, $1.1\cdot10^{-3}$ mol) in Et_2O (4.4 ml) kept under nitrogen at 0°C, and the mixture was stirred for 30 min at the same temperature. Once the mixture was cooled at −78°C, a solution of **11** (0.28 g, $1.0\cdot10^{-3}$ mol) in THF (4 ml) was added dropwise and the mixture was stirred for 30 min at the same temperature. Then, a solution of **21** (0.62 g, $3.0\cdot10^{-3}$ mol) in THF (4 ml) was added and the mixture was stirred at 0°C for 5 h. After this time, the reaction mixture was diluted in CH_2Cl_2 (30 ml) and washed with sat. NH_4Cl (3× 30 ml). The organic layer was dried with $MgSO_4$, the solvents were evaporated, and the resulting product was purified by column chromatography (230−400 mesh silica gel; eluant: EtOAc/hexane, 1:14) to give 0.17 g of **22** (60%). Colorless oil. − $[\alpha]_D^{25}$ = +41.4 (*c* = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 1807 cm^{-1} (C=O), 1712 (C=O). − ^1H NMR ($CDCl_3$): δ = 1.04 [d, J = 6.7 Hz, 3 H, C*H*$(CH_3)_2$], 1.12 [d, J = 6.7 Hz, 3 H, C*H*$(CH_3)_2$], 1.36 [s, 9 H, C(C*H*$_3)_3$], 2.05−2.15 [m, 1 H, CH(C*H*$_3)_2$], 2.85 [dd, *J* = 3.1, 9.1 Hz, 1 H, C*H*CH$(CH_3)_2$], 4.63 (d, *J* = 3.1 Hz, 1 H, C*H*Ph), 7.25−7.41 (m, 5 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 20.0, 20.4, 27.8, 28.6, 58.7, 66.3, 83.1, 125.8, 128.2, 128.8, 138.5, 147.8, 167.6. − MS (70 eV) *m/z* (%): 189 (3.4) [M^+ − 100], 146 (42.8), 131 (100.0).

Preparation of **23**: The general procedure described in ref.[22b] was followed starting from **22** (0.14 g, $0.5\cdot10^{-3}$ mol). The resulting carboxylic acid was methylated quantitatively with diazomethane to afford 0.08 g (60%, overall), colorless oil. − $[\alpha]_D^{25}$ = +51.3 (*c* = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 1814 cm^{-1} (C=O), 1748 (C=O), 1725 (C=O). − ^1H NMR ($CDCl_3$): δ = 1.04 [d, *J* = 6.7 Hz, 3 H, C*H*$(CH_3)_2$], 1.10 [d, *J* = 6.7 Hz, 3 H, C*H*$(CH_3)_2$], 1.51 [s, 9 H, C(C*H*$_3)_2$], 2.05−2.15 [m, 1 H, CH(C*H*$_3)_2$], 2.01−2.20 [m, 1 H, C*H*$(CH_3)_2$], 2.98 [dd, *J* = 3.1, 8.5 Hz, 1 H, C*H*CH$(CH_3)_2$], 3.81 (s, 3 H, OCH_3), 4.14 (d, *J* = 3.1 Hz, 1 H, C*H*CO_2CH_3). − ^{13}C NMR ($CDCl_3$): δ = 19.8, 20.0, 27.9, 28.1, 52.6, 53.9, 61.9, 83.8, 145.2, 164.9, 169.9. − MS (70 eV); *m/z* (%): 216 (1.4), 128 (100.0), 96 (30.6).

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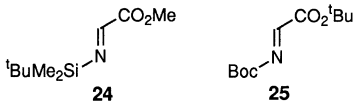
[18] Crystal data for compound **15**: $C_{40}H_{42}N_2O_8$, M_r = 678.76, monoclinic, space group $P2_1$, a = 9.926(5), b = 8.007(5), c = 23.31(7) A, β = 101.86(7)° V = 1813(6) A^3, Z = 2, D_x = 1.24 Mg m^{-3}, Mo$_s$-K_α radiation (graphite crystal monochromator, λ = 0.71073 A), μ = 0.087 cm^{-1}, F(000) = 720, T = 293 K. Final conventional R = 0.052 [for 1938 $F_o > 4\sigma(F_o)$], and $wR2$ = 0.123 (for all reflections), $w = 1.0/[\sigma^2(F_o^2) + (0.0538 \cdot P)^2]$ where $P = [\mathrm{Max}(F_o^2,0) + 2 \cdot F_c^2]/3$. Total number of parameters 451. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crytallographic Data Centre as supplementary publication no. CCDC-101498. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

[19] The reaction of Me_2CuLi with imine **10** in THF at 0°C for 3 h did not afford any imine addition compound and the polymerization of the imine was observed instead. For recent reviews on domino reactions, see: [19a] L. F. Tietze, U. Beifuss, *Angew. Chem*. **1993**, *105*, 137−170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131−163. − [19b] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115−136.

[20] The reaction of the activated imines **24** and **25** with Me_2CuLi and Michael acceptor **11** at 0°C was also examined.



24 **25**

While **24** gave the expected mixture of *cis*- and *trans*-β-lactams (57:43) in very poor yield (< 10%), **25** gave a 50:50 mixture of the corresponding β-*N*-Boc-aminoamides, which did not cyclize to the corresponding β-lactams. For a related two-component reaction of activated imines with enolates from chiral *N*-acyloxazolidinones and Oppolzer′s camphorsultam derivatives, see: [20a] I. Abrahams, M. Motevalli, A. J. Robinson, P. B. Wyatt, *Tetrahedron* **1994**, *50*, 12755−12772. − [20b] A. M. Kanazawa, J.-N. Denis, A. E. Greene, *J. Org. Chem*. **1994**, *59*, 1238−1240.

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