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Asymmetric Synthesis of δ-Substituted α,β-Unsaturated δ-Lactams by Ring Closing Metathesis of Enantiomerically Pure *N*-Acryloyl-homoallylic Amines

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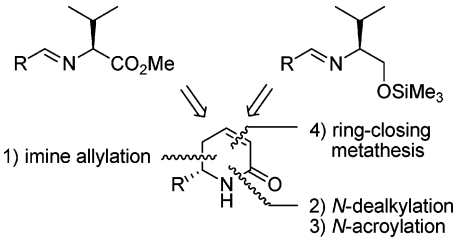

Optically pure secondary homoallylic amines, obtained by highly diastereoselective addition of allylmetal reagents to imines derived from chiral amines, were N-dealkylated, and the primary amines were converted to *N*-acryloyl amides. Then, ring closing metathesis gave δ-substituted δ-lactams in good overall yields.

Introduction

The ring closing metathesis (RCM) of 1,*n*-dienes is a powerful and versatile technique for the construction of carbocyclic and heterocyclic compounds.[1] In particular, this methodology has been exploited for the synthesis of azaheterocycles, as witnessed by several reviews dealing with the synthesis of natural compounds (e.g., piperidine and pyrrolidine alkaloids,[2,3] dipeptide mimetics,[4] and β-lactams of non-classical structure).[5] The required azadiene for the RCM reaction can be prepared by a plethora of methods. A simple route involves the addition of an unsaturated organometallic reagent to an imine and the subsequent N-alkylation with an unsaturated alkyl halide. In this case, asymmetric induction in the carbon−carbon bond formation (imine addition) can be achieved by three different methodologies exploiting (a) substrate induced diastereoselectivity (SID),[6] where the chirality is present in the imine, generally in the C-substituent, and is retained in the product; (b) auxiliary induced diastereoselectivity (AID), where the chirality is present in the imine, generally in the N-substituent, that is removed in a successive step; and (c) reagent induced stereoselectivity (RIS),[7] where the asymmetric induction is provided by a chiral ligand that is bound to the metal by covalent bond(s) or by Lewis acid−base interaction(s).

The AID approach to the synthesis of substituted piperidines is illustrated in Scheme 1. It involves the C-allylation of chiral imine **1** to give the homoallylic amine **2** and successive N-allylation to give the 5-aza-1,7-diene **3**. The absolute configuration of the new stereocenter α to N formed in the allylmetalation step is controlled by the chiral auxiliary (N-

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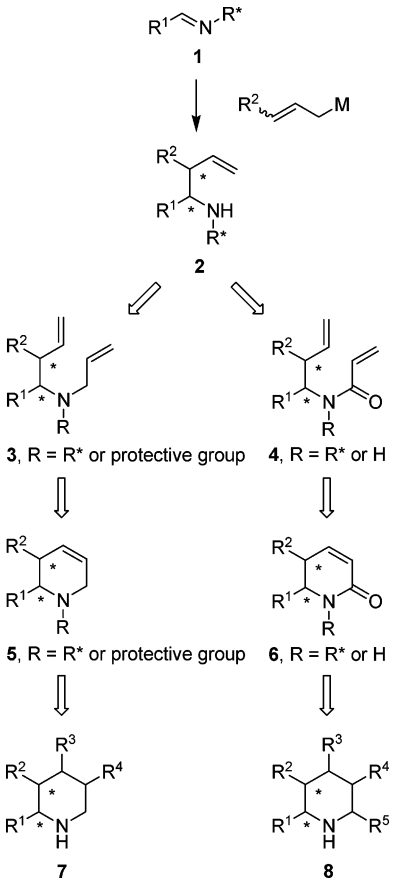
SCHEME 1



substituent). When the allylmetal reagent bears a γ-substituent (R^2), two stereocenters are formed, whose relative stereochemistry is determined by the (*E*) or (*Z*) geometry of the substituted allylmetal reagent. In the first report of this approach,[8] (−)-pipecoline, (−)-coniine, and (−)-2-phenylpiperidine were synthesized beginning from imines derived from (*R*)-1-phenylethylamine and acetaldehyde, butyraldehyde, and benzaldehyde, respectively, exploiting in the first step the zinc-mediated Barbier allylation procedure we previously developed for imines derived from (*S*)-valine esters.[9] After N-allylation of the homoallylic amines **2** thus obtained gave **3** (R = R*), the RCM reaction catalyzed by the first generation Grubbs ruthenium benzylidene complex afforded the tetrahydropyridines **5** (R = R*) as a mixture of diastereomers (d.r. <85:15), which were separated by column chromatography. Finally, hydrogenation of the alkene and concomitant hydrogenolysis of the N-substituent afforded the piperidines **7** (R^2 to R^4 = H). (−)-Coniine and (*R*)-2-phenylpiperidine also have been synthesized by an analogous route that used (*S*)- and (*R*)-(*O*)-(1-phenylbutyl)hydroxylamine as the chiral auxiliaries in the appropriate oximes, which underwent the addition of allylmagnesium bromide with good stereocontrol (de 87 and 91%, respectively).[10] A longer route involves the removal of the chiral auxiliary from the homoallylic amine **2**, protection of the amine function (e.g., as a carbamate), N-allylation to give the N-protected azadiene **3**, RCM to give the N-protected tetrahydropyridine **5**, hydrogenation, and final N-deprotection.[10] *N*-Acetyl-(−)-coniine was similarly prepared in seven steps; in the first of them, the addition of lithiated allyl phenyl sulfone to enantiopure *N*-*p*-toluenesulfinyl butyraldimine occurred with low diastereoselectivity, affording a mixture of three diastereomeric branched homoallylic amines with a 1:1:3 ratio.[11,12]

On the basis of these reports, we considered that there was room for improvement. Above all, we foresaw a significant variant in the synthetic sequence by the conversion of the secondary homoallylic amine **2** to the acryloyl amide **4** (Scheme 1), as the *N*-acryloyl substituent provides at the same time a two carbon fragment to the ring being constructed and acts as a protective group of the amine function in the RCM step leading to the α,β-unsaturated δ-lactams **6**. The latter compounds are precursors of the saturated piperidines **8** by a plethora of methodologies.

α,β-Unsaturated δ-lactams have been previously prepared by RCM reactions.[13,14] For example, an unsymmetrically δ,δ-disubstituted α,β-unsaturated δ-lactam, precursor of a disubstituted piperidine NK_1 antagonist, was prepared from *N*-(*t*-butylsulfinyl)ketimine by a route analogous to that described in Scheme 1, involving the addition of allylmagnesium chloride (63% yield, d.r. 9:1).[13k] Alternatively, homoallylic amines were prepared from optically pure homoallylic alcohols through substitution by an azide ion in HMPA,[13f] and by the addition of vinylmagnesium chloride to (*S*)-*N*-Boc-phenylalaninal,[13n] then, in both cases, reaction with acryloyl chloride and RCM reaction led to polysubstituted lactams.

In principle, following routes analogous to those described in Scheme 1, either the size and/or the position of the double bond of the unsaturated lactams can be varied by the proper choice of the ω-alkenylmetal reagent and the ω-alkenyl/alkenoyl halide. However, the synthesis of six-membered rings takes

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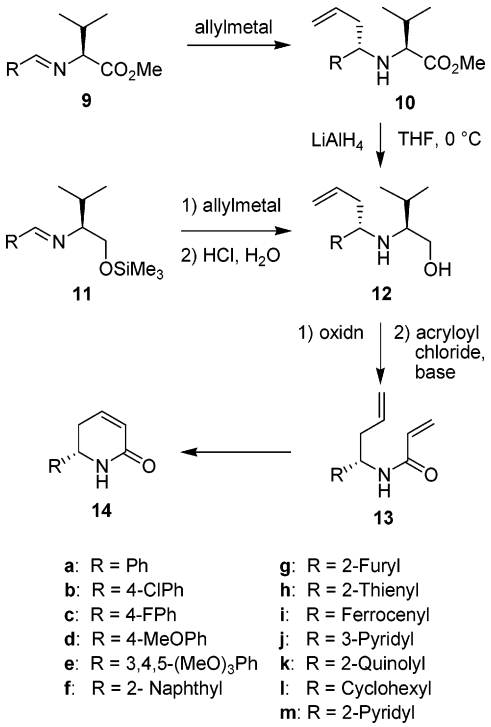
advantage of the higher reactivity and ready availability of the allylic organometallic reagents and allyl/acryloyl halides. In this paper, we describe the successful synthesis of δ-substituted α,β-unsaturated δ-lactams by the general route described in Scheme 1 (**1** to **6** through **4**).[15] It is worthwhile observing that although a plethora of methods is available for the synthesis of α,β-unsaturated δ-lactams,[16] we could find in the literature only a few reports of optically pure δ-substituted α,β-unsaturated δ-lactams **6**, having R^1 = (*R*)-CO_2Me,[13a] (*S*)-CO_2Me,[16a] (*R*)-[(3*R*,5*S*)-1-Cbz-5-(acetoxymethyl)piperidin-3-yl),[13e] (*S*)-CH_2-CO_2Me,[13k] (*S*)-*n*-$C_{15}H_{31}$,[13l] (*S*)-CO_2H,[16u] and (*S*)-CO_2tBu (*N*-Boc derivative).[16t]

Obviously, the usefulness of our synthetic route is based on the capability of achieving the highest possible diastereoselectivity in the first allylmetalation step. In this respect, the choice of the chiral auxiliary (amine) is of paramount importance and should be based also on the nature of the starting aldehyde.[17] A variety of optically pure primary amines (including amino acid esters and amides and β-amino alcohols), hydrazines, hydroxylamines, and sulfinamides is available for this purpose, and each of them often provides an excellent diastereoselectivity in organometallic additions, particularly with allylmetal reagents, as thoroughly described in recent reviews.[17,18]

Results and Discussion

The actual route followed for the synthesis of δ-substituted α,β-unsaturated δ-lactams is described in Scheme 2. In particular, we exploited (*S*)-valine methyl ester for the preparation of the homoallylic amines **13** from the precursor imines **9**. We previously achieved high to complete stereocontrol in this crucial step by the addition of allylcopper, -tin, -lead, and -zinc reagents to a variety of aromatic and aliphatic imines in anhydrous tetrahydrofuran (THF) at low temperature (Grignard protocol).[19]

SCHEME 2



We also described a convenient Barbier protocol, which relies on the reaction of imines with allyl bromide and zinc and a catalytic amount (generally 10 mol %) of cerium trichloride heptahydrate in anhydrous THF at 0 °C.[9] The hydrated cerium salt may have different roles in the process, but above all, it prevents the retroallylation reaction, so preserving the stereochemical purity of the homoallylic zinc amide produced. As a matter of fact, complete or almost complete diastereoselectivities were obtained with aromatic and aliphatic imines (e.g., the benzaldimine **9a**). Subsequently, other authors reported that this Barbier protocol worked efficiently and diastereoselectively with substituted allylic bromides and with 4-hydroxybenzaldimine and its O-substituted derivatives, suitable substrates for the preparation of supported chiral catalysts.[20] More recently, the same procedure has been efficiently applied to imines derived from 2-thiophenecarboxaldehyde and several α-aminoacid esters, as well as **9h**; moreover, such addition reactions employing diimines or triimines with a polycyclic aromatic core produced chiral multiallylic dendritic amines with a similar diastereoselectivity.[21] On this basis, we decided to implement the stereoselective synthesis of new homoallylic amines **10b**−**l** by applying our Barbier protocol to the imines **9b**−**l**, derived from either aromatic and aliphatic aldehydes. The primary homoallylic amine precursors of **13a**−**l** were then obtained by efficient reduction of the ester group by lithium aluminum hydride to give the intermediate aminoalcohols **12** and removal of the N-substituent (Scheme 2 and Table 1).

The results of the Barbier allylmetalation of imines **9a**−**l**, derived from the valine methyl ester, are reported in Table 1. In almost all cases, as expected, we observed complete or almost

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TABLE 1. Synthesis of Secondary Homoallylic Amines 10[a] and β-Aminoalcohols 12[b] from Imines 9

imine **9**, R	**10**	d.r.[c]	yield (%)[d]	**12** from **10** (yield %)[d]
9a, Ph	**10a**	100:0	86	98
9b, 4-ClPh	**10b**	>99:1	78	98
9c, 4-FPh	**10c**	>99:1	80	92
9d, 4-MeOPh	**10d**	>99:1	87	98
9e, 3,4,5-$(MeO)_3$Ph	**10e**	>99:1	76	94
9f, 2-naphthyl	**10f**	>99:1	91	100
9g, 2-furyl	**10g**	>99:1	65	92
9h, 2-thienyl	**10h**	>99:1	86	100
9i, ferrocenyl	**10i**	>99:1[e]	80[f]	100
9j, 3-pyridyl	**10j**	>99:1	88	71
9k, 2-quinolyl	**10k**	66:34	95[g]	
9l, cyclohexyl	**10l**	>99:1	79	90

[a] Reactions were performed on 5−10 mmol of imine by the Barbier protocol using allylBr (1.5 equiv), Zn (2 equiv), $CeCl_3$-$7H_2O$ (0.1 equiv), THF, 0 °C, 1 h. [b] Reaction conditions: $LiAlH_4$ (2 equiv vs **10**), THF, −10 °C, 1 h. [c] Determined by GC-MS and ^{1}H NMR analysis of the crude product. [d] Yield of product isolated by flash chromatography. [e] Product was not eluted by GC-MS; an impurity, detected in <5% amount by ^{1}H NMR analysis, could not be identified. [f] Pure diastereomer was obtained by crystallization of the crude product from MeOH. [g] No attempt was made to separate the diastereomers.

complete diastereoselectivity (d.r. >99:1) and high yield of the desired homoallylic amines **10**, which were purified from small amounts or traces of starting materials and, especially for the reaction on the *p*-fluorophenylimine **9c**, products coming from over-reaction (attack on the ester group). A low diastereoselectivity was obtained with the 2-quinolineimine **9k** (d.r. 66:34), and no attempt was made to separate the two diastereomers.

The low stereocontrol obtained with **9k** is in accord with the outcomes of organometallic additions to analogous 2-pyridineimines and can be explained by the capability of these imines to form N,N′-chelated complexes with the organometallic reagent in competition with the rigid N,O-chelated complexes that can be formed by the intervention of the chiral auxiliary. In the N,N′-chelated complexes, the N-substituent (chiral auxiliary) is free to rotate along the N−C* bond, so increasing the number of reactive conformers.

We previously reported that valine methyl ester is not the best auxiliary for the addition of the preformed allylmetal reagent to 2-pyridineimine at low temperature. The allylation reaction carried out by cerium-catalyzed or other Barbier protocols gave even worse results in terms of diastereoselectivity. We also reported that *O*-silyl-protected (*S*)-valinol was an excellent and convenient chiral auxiliary for the addition of organolithium, Grignard, and organozincate reagents to the imines **11**.[22] In particular, it provided better stereocontrol than valine esters for the allylzincation of bidentate imines, especially those derived from 2-pyridinealdehyde. Protection of the valinol OH group is opportune, otherwise, an excess of organometallic reagent, a longer reaction time, and a higher temperature are required, and consequently, a lower diastereoselectivity is often obtained, as we observed, for example, in the Zn-mediated Barbier reaction on the benzaldimine **10a**.[9a]

It should also be noted that the *O*-silyl protection is easily introduced, as well as easily removed, to obtain the secondary homoallylic amines **12** by a simple acidic hydrolysis or treatment with ammonium fluoride in protic solvent; hence, it is more conveniently used than the *O*-methyl or *O*-benzyl protections reported by other authors.[13,18] Moreover, the valinol-derived N-substituent can be directly removed from the amine **12** by an oxidative cleavage, whereas reduction of the ester group step of the secondary amine **10** is an additional step when starting from the imine **9**. Hence, we carried out the allylmetalation of the 2-quinolineimine **11k** using either allylzinc bromide or allylmagnesium chloride (Table 2). However, the homoallylic amine **12k** was obtained with a diasteromeric ratio not exceeding 90:10 after a routine desilylation step, markedly differing from the almost complete diastereoselectivity obtained for the 2-pyridine derivative **12m**.[22a] The prevalent diastereomer was then isolated in moderate yield by column chromatography.

TABLE 2. Synthesis of β-Aminoalcohols 12k,m[a] from Imines 11k,m

imine **11**, R	allylmetal	**12**	d.r.[b]	yield (%)[c]
11k, 2-quinolyl	allylZnBr	**12k**	80:20	45
11k, 2-quinolyl	allylMgCl	**12k**	90:10	45
11m, 2-pyridyl	allylMgCl[d]	**12m**	99:1	87

[a] Reactions were performed on 5−10 mmol of imine; allylmetal (2 equiv), THF, −78 °C, 3 h. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Yield of the pure prevalent diastereomer isolated by column chromatography. [d] Reaction described in ref 22a.

TABLE 3. Two-Step Preparation of Acryloyl Amides 13 from β-Aminoalcohols 12

12, R	method[a]	product **13**	yield (%)[b]
12a, Ph	A	**13a**	74
12b, 4-ClPh	A	**13b**	75
12c, 4-FPh	A	**13c**	78
12d, 4-MeOPh	A	**13d**	87
12e, 3,4,5-$(MeO)_3$Ph	A	**13e**	77
12f, 2-naphthyl	A	**13f**	90
12g, 2-furyl	B	**13g**	80
12h, 2-thienyl	B	**13h**	67
12i, ferrocenyl	A	**13i**	87
12j, 3-pyridyl	A	**13j**	70
12k, 2-quinolyl	B	**13k**	69
12l, cyclohexyl	C	**13l**	62
12m, 2-pyridyl	B	**13m**	50

[a] Method A: (1) H_5IO_6, $MeNH_2$, MeOH and (2) acryloyl chloride, Na_2CO_3, acetone. Method B: (1) H_5IO_6, $MeNH_2$, MeOH and (2) acryloyl chloride, triethylamine, DMAP (cat.). Method C: (1) lead tetraacetate and hydroxylamine hydrochloride and (2) acryloyl chloride, Na_2CO_3, acetone. [b] Yield of pure product after column chromatography.

The diastereomerically pure β-aminoalcohols **12** were then subjected to cleavage of the auxiliary group (N-substituent) by an oxidative protocol using periodic acid in the presence of methylamine. The crude primary homoallylic amines were not purified but instead were directly converted to *N*-acryloyl amides **13** by routine procedures using acryloyl chloride and different bases (i.e., sodium carbonate in acetone (procedure A) or triethylamine in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP)). Only in the case of the aliphatic amine **12l** was the cleavage of the N-substituent preferably achieved with lead tetraacetate (LTA), and the primary amine was then reacted with acryloyl chloride/sodium carbonate/acetone (procedure C). By these two-step procedures, the unsaturated amides **13** were obtained with good overall yields (Table 3).

The unsaturated amides **13** were then subjected to the RCM reactions to prepare the six-membered α,β-unsaturated lactams **14** (Scheme 2) exploiting the commercially available, widely

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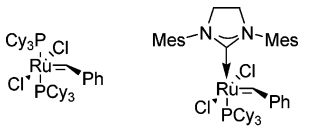
TABLE 4. Synthesis of δ-Substituted α,β-Unsaturated δ-Lactams 14 by RCM of *N*-(3-Buten-1-yl) Acryloyl Amides 13[a]

acryloyl amides **13**	II (mol %)	solvent	additive (equiv)	lactam	yield (%)[b]
13a, Ph	5	CH_2Cl_2		**14a**	76
13b, 4-ClPh	5	CH_2Cl_2		**14b**	72
13c, 4-FPh	5	CH_2Cl_2		**14c**	77
13d, 4-MeOPh	5	CH_2Cl_2		**14d**	77[c]
13e, 3,4,5-$(MeO)_3$Ph	5	CH_2Cl_2		**14e**	69[c]
13f, 2-naphthyl	5	CH_2Cl_2		**14f**	80[c]
13g, 2-furyl	5	CH_2Cl_2		**14g**	60
13h, 2-thienyl	5	CH_2Cl_2		**14h**	62
13i, ferrocenyl	5	CH_2Cl_2		**14i**	78
13j, 3-pyridyl	5	CH_2Cl_2		**14j**	0
13j, 3-pyridyl	5	CH_2Cl_2	TFA (2.5)	**14j**	70
13k, 2-quinolyl	5	CH_2Cl_2	TFA (2.5)	**14k**	0
13k, 2-quinolyl	10	benzene		**14k**	40[d]
13l, *c*-Hx	5	CH_2Cl_2		**14l**	82
13m, 2-pyridyl	5	CH_2Cl_2	TFA (2.5)	**14m**	0
13m, 2-pyridyl	5	CH_2Cl_2	HCl (1)	**14m**	0
13m, 2-pyridyl	10	benzene	TFA (2.5)	**14m**	0

[a] Reactions were carried out using the Grubbs' catalyst **II** for 3 h at the reflux temperature of the solvent. [b] Yield of product purified by column chromatography. [c] Using 2 mol % of the catalyst incomplete ring closure was observed after 3 h. [d] About 80% conversion of the starting diene was determined by ^{1}H NMR analysis.

used ruthenium benzylidene complexes (i.e., the first and second generation Grubbs' catalysts **I** and **II**, respectively). Preliminary attempts carried out using **I** were not satisfactory, whereas **II** generally performed well, so the latter catalyst was chosen for the subsequent reactions. The results of the metathesis reactions performed on the unsaturated amides **13** are reported in Table 4.

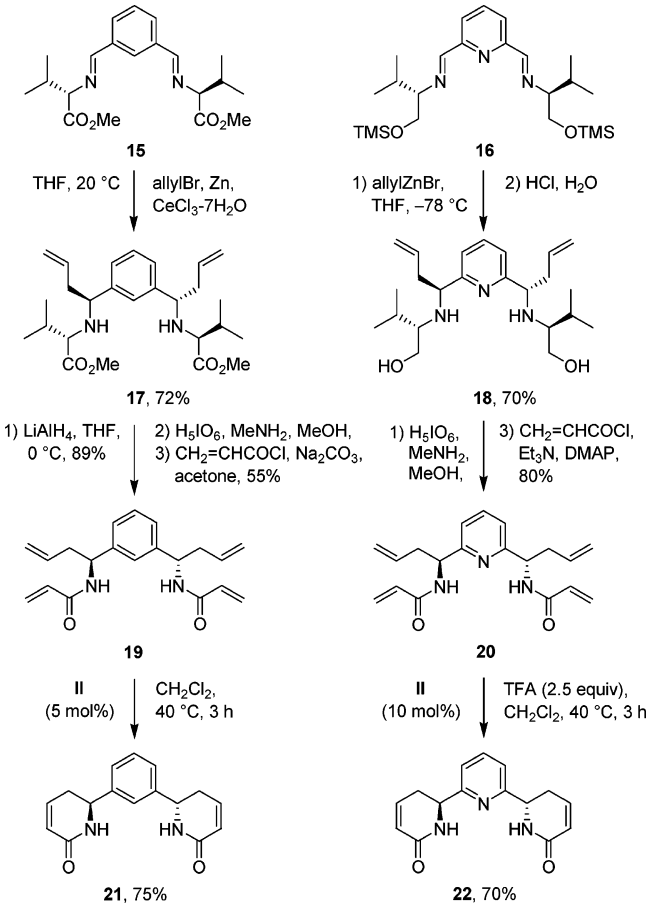


I **II**

In most cases, good results were obtained by working with 5 mol % of catalyst in dichloromethane solution at the reflux temperature. Following the progress of the reaction by TLC or GC-MS analysis, the disappearance of the starting compound **13** was observed after 3 h. After usual workup, the expected products **14** were isolated in good yields after separation from minor amounts of byproducts by medium-pressure column chromatography. However, in the case of pyridyl containing substrates, the reaction did not work in the usual conditions. The 3-pyridyl derivative **13j** could be converted to the corresponding unsaturated lactam **14j** in 70% yield only in the presence of 2.5 equiv of trifluoroacetic acid (TFA). However, for the 2-quinolyl and 2-pyridyl derivatives **13k** and **13m**, respectively, even the latter conditions did not allow for their satisfactory conversion. Surprisingly, the 2-quinolyl-substituted lactam **14k** was obtained in 40% yield by working in refluxing benzene in the absence of TFA. Instead, the 2-pyridyl-substituted lactam **14m** could not be obtained from **13m** working either in dichloromethane in the presence of TFA or HCl or in benzene in the presence of TFA.

It should be observed that the furyl-substituted lactam **14g** can be converted to the carboxy-substituted analogue **14** (R = CO_2H, Scheme 2) and then the corresponding ester[13a] via routine oxidation of the furan ring.[22b] Similarly, Nickel−Raney reduction/desulfurization of the thiophene ring[23] of **14h** would lead to the *n*-butyl-substituted lactam **14** (R = *n*-Bu, Scheme 2); this route should be preferable to the alternative one beginning from pentaneimines **9** or **11** (R = *n*-Bu, Scheme 2), as linear aliphatic aldimines are less easily prepared than aromatic imines.

SCHEME 3



The synthetic sequence described for the preparation of δ-aryl-δ-lactams from mono-imines was then applied to the synthesis of the C_2-symmetric dilactams **21** and **22**, where the two rings are connected through a 1,3-disubstituted benzene ring or 2,6-disubstituted pyridine ring (Scheme 3). The diimine **15** derived from isophtalaldehyde and the (*S*)-valine methyl ester was allylated by the Barbier protocol and gave the expected di-homoallylic amine **17** in good yield and with almost complete diastereoselectivity. Reduction of the ester groups to alcohol, oxidative cleavage, and reaction of the primary amines with acryloyl chloride gave the unsaturated diamide **19**, and then RCM gave the dilactam **21** in satisfactory overall yield. On the other hand, the imine **16** was prepared by condensation of 2,6-pyridinedicarbaldehyde and (*S*)-valinol, followed by silylation of the hydroxyl groups. The Grignard protocol using allylzinc bromide at low temperature gave the di-homoallylic amine **18** with d.r. 96:4, and the pure prevalent diastereomer was obtained in 70% yield after column chromatography. Removal of the chiral auxiliaries and N,N′-diacroylation gave the unsaturated diamide **20**. We were delighted, and surprised, to observe that the double RCM reaction in the presence of TFA (2.5 equiv) was successful for this compound, despite the failure previously

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observed for the mono-amide **13m**, although an increased amount of catalyst (10 mol %) was required to obtain the dilactam **22** in a satisfactory yield. Actually, we cannot explain the positive effect of TFA in the latter reaction.

Conclusion

The stereoselective synthesis of simple δ-substituted α,β-unsaturated δ-lactams has been accomplished starting from readily available materials: aldehydes, optically pure primary amines, allyl halides (allylmetal compounds), and acryloyl chloride, which were assembled by established methodologies allowing the easy and efficient formation of a carbon−nitrogen bond (imine formation) and three carbon−carbon bonds. In particular, the highly diastereoselective formation of the C5−C6 bond has been accomplished by two alternative protocols for the allylmetalation of chiral imines, which were obtained from (*S*)-valine methyl ester or (*S*)-valinol. Then, after removal of the N-substituent and N-acroylation of the primary homoallylic amine, the unsaturated lactam ring was built by a ring closing metathesis reaction.

As noted in the Introduction, a C5 substituent could be introduced diastereoselectively by using a γ-substituted allylmetal reagent, so forming two new stereocenters by combined auxiliary induced and simple diastereoselectivities. Moreover, the versatility of this route is further enhanced by the possibility of using the unsaturated lactams to construct more substituted/functionalized nitrogen heterocycles as the conjugated alkene and amide functions can undergo further transformations. For example, nucleophilic conjugate addition and reduction of the lactam carbonyl group can be sequentially used to prepare *cis*- and/or *trans*-2,4-disubstituted piperidines,[24] a structural motif that is present in a number of biologically and pharmacologically active compounds.[25]

It should also be remarked that the C_2-symmetric 2,6-disubstituted pyridine **22** is an appealing compound, with potential utility as a ligand in asymmetric synthesis and catalysis, for two reasons. First of all, owing to the presence of the basic pyridine nitrogen, it is capable of coordinating a metal center in either bidentate and terdentate fashion. Second, the acidity of the N−H lactam bonds could be exploited in asymmetric catalytic reactions involving the formation of metal amide(s) intermediates. Moreover, there is ample scope to convert **22** to a series of *N*,*N*,*N*-terdentate ligands by transformations of the α,β-unsaturated lactam groups.

Experimental Section

The following compounds have been previously described: **9a**, **9d**,[9b] **9h**,[21] **9k**,[22c] **10a**,[9b] **10d**,[9b] **10h**,[21] **10j**,[9b] **12a**,[9b] **12g**,[22b] and **16**.[22d] The preparation of racemic lactams **13a**[26] and **14a**[16c] has been previously reported. The novel imines were prepared by the same procedures described previously.

Barbier Allylation of Imines 9. Zinc dust (1.31 g, 20 mmol) was added in small portions to a solution of the imine **9** (10 mmol), allyl bromide (1.8 g, 1.3 mL, 15 mmol), and $CeCl_3 \cdot 7H_2O$ (0.372 g, 1 mmol) in anhydrous THF (15 mL) at 0 °C, and the mixture was then stirred at room temperature. The reactions were monitored by TLC and GC-MS analyses and were usually complete within 1.5 h. To the mixture was added saturated aqueous NH_4Cl (10 mL) and 40% NH_3 (10 mL), and the organic phase was extracted with Et_2O (2 × 15 mL). The combined ethereal layers were dried over Na_2SO_4 and concentrated at reduced pressure to give an oily residue, which was subjected to flash chromatography eluting with cyclohexane/ethyl acetate mixtures. Starting from the diimine **15**, 2-fold amounts of reagents were required.

Reduction of Amino Esters 10 with $LiAlH_4$. A solution of the amino ester **10** (5 mmol) in anhydrous THF was added dropwise to a suspension of $LiAlH_4$ (0.38 g, 10 mmol) in THF (10 mL) and cooled with an ice/NaCl bath. After 1 h, the reaction was quenched with 2.5 M NaOH (10 mL) (*Caution: this is a very exothermic reaction*) and then H_2O (10 mL), and the organic phase was extracted with Et_2O (2 × 15 mL). The combined ethereal layers were dried over Na_2SO_4 and concentrated at reduced pressure to give the products **12**, which were used as obtained in the successive step. Starting from **17**, 2-fold amounts of reagents were required.

Organometallic Addition to Imines 11 and 16. A solution of allyl bromide (1.3 mL, 1.8 g, 15 mmol) in anhydrous THF (20 mL) was added dropwise to a stirred suspension of zinc dust (1.31 g, 20 mmol) in THF (8 mL). The reaction was exothermic, and the rate of addition must be controlled to maintain the temperature below 50 °C. After the addition was complete, the mixture was stirred for 1 h and then stirring was stopped to allow the zinc dust to deposit on the bottom of the flask. The solution was taken by a syringe and transferred into an addition funnel and finally added dropwise to a solution of the imine **11** (5 mL) in dry THF cooled at −78 °C. The reaction was monitored by TLC and GC-MS analyses, and the *O*-trimethylsilyl amino alcohol was obtained by the usual workup. The crude product was dissolved in Et_2O (5 mL) and treated with 1 M HCl (10 mL) for 1 h, then 2.5 M NaOH was added until pH 11 was reached, and the organic material was extracted with Et_2O (2 × 10 mL). The combined ethereal layers were dried over Na_2SO_4, concentrated at reduced pressure, and subjected to flash chromatography eluting with cyclohexane/ethyl acetate mixtures. Starting from the diimine **16**, 2-fold amounts of reagents were required.

Preparation of Propenamides from β-Amino Alcohols. Procedure A. The amino alcohols **12a**−**j** (1 mmol) were dissolved in a mixture of MeOH (15 mL) and THF (5 mL), then 40% aqueous $MeNH_2$ (12 mL) was added. A solution of H_5IO_6 (0.80 g, 3.5 mmol) in H_2O (15 mL) was added dropwise with stirring. The reaction was slightly exothermic. The reaction was monitored by TLC and GC-MS analyses. When the reaction appeared complete (1−3 h), the mixture was concentrated at reduced pressure to remove most of the MeOH, and H_2O (15 mL) was added. The organic phase was extracted with Et_2O (2 × 20 mL), and the combined ethereal layers were dried over Na_2SO_4 and concentrated at reduced pressure. The residue was dissolved in acetone, and Na_2CO_3 (0.37 g, 3 mmol) dissolved in 5 mL of H_2O was added. To the vigorously stirred mixture, at 0 °C, was added dropwise acryloyl chloride (0.18 g, 163 μL, 2 mmol) dissolved in acetone (10 mL). The reaction was monitored by TLC and GC-MS analyses, and when it appeared complete (ca. 2 h), most of the solvent was evaporated at reduced pressure, H_2O (15 mL) was added, and the organic phase was extracted with Et_2O (2 × 15 mL). The combined ethereal layers were dried over Na_2SO_4 and concentrated at reduced pressure, and

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the residue was subjected to flash chromatography to give the pure amides **13a**−**j**. Compound **19** was similarly obtained from **17** by using 2-fold amounts of reagents.

Procedure B. Cleavage of the N-substituent of **12k**,**m** was conducted as described previously, then the crude primary amine was dissolved in THF (10 mL), and triethylamine (0.15 g, 0.21 mL) and DMAP (0.01 g) were added. To the vigorously stirred mixture at 0 °C was added dropwise acryloyl chloride (0.13 g, 0.12 mL, 1.5 mmol) dissolved in THF (10 mL), and a white precipitate formed immediately. The reaction was monitored by TLC and GC-MS analyses. The solvent was removed at reduced pressure, and the crude product was subjected to flash chromatography to give the pure amide **13k**,**m**. Compound **20** was similarly obtained from **18** by using the proper amounts of reagents.

Procedure C. The amino alcohol **12l** (0.63 mmol) was dissolved in a 1:1 MeOH/CH_2Cl_2 mixture (6 mL), and then lead tetraacetate (0.33 g, 0.75 mmol) was added to the stirred solution and cooled to 0 °C. When TLC analysis showed complete consumption of the starting material, hydroxylamine hydrochloride (0.04 g, 6.3 mmol) was adde, and the mixture was vigorously stirred for 3 h. H_2O (5 mL) was added, and the insoluble material was filtered off, then the organic phase was extracted with Et_2O (2 × 10 mL). The combined ethereal layers were dried over Na_2SO_4 and concentrated at reduced pressure to yield the crude primary amine, which was converted into the amide **13l** as described in procedure A.

Preparation of α,β-Unsaturated δ-Lactams. The unsaturated amide (1 mmol) was dissolved in anhydrous CH_2Cl_2 or C_6H_6 (5 mL), and TFA (0.29 g, 192 μL, 2.5 mmol) was added for **13j**,**k** and **20**. The solution was degassed by bubbling a stream of Ar through it, Ru-complex **II** (0.042 g, 0.05 mmol) was added, and the solution was again deaerated and heated to reflux. The progress of the reaction was monitored by TLC analysis, and the disappearance of the starting material was observed within 3 h. The solvent was removed at reduced pressure, and the residue was subjected to flash chromatography.

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Supporting Information Available: General methods, analytical data, and copies of ^1H and ^{13}C NMR spectra for all new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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