Pergamon

Tetrahedron Letters 40 (1999) 585–588

TETRAHEDRON LETTERS

A Novel Asymmetric Synthesis of 2-Azetidinones from Achiral Precursors

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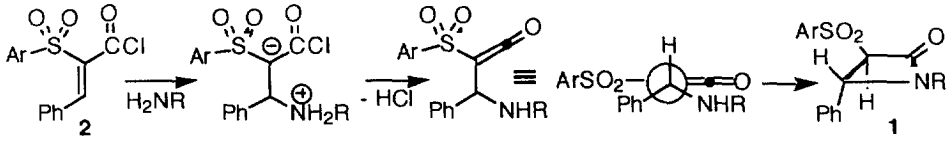
Received 9 September 1998; revised 6 November 1998; accepted 12 November 1998

Abstract: Asymmetric synthesis of (3*S*,4*S*)-3-phenylsulfonyl-4-phenylazetidin-2-ones in up to 46% ee from achiral amines and 2-phenylsulfonyl-3-phenylpropenoyl chloride was achieved with chiral Lewis-acid catalysis by salen-copper(II) complexes derived from (1*R*,2*R*)-(-)-1,2-diaminocyclohexane. The absolute configuration was assigned by single crystal, X-ray crystallographic analyis of enantiomerically pure (3*S*,4*S*)-(-)-3-phenylsulfonyl-4-phenylazetidin-2-one (**7**).

We have recently described a new synthetic approach to *trans*-3-arylsulfonyl-4-phenyl-2-azetidinones **1** as shown in Scheme 1.[1] The 1,4-addition of amines to 2-arylsulfonyl-3-phenylpropenoyl chlorides **2** is much faster than competing 1,2-addition to the acid chloride. From the kinetics of reaction, we invoke a ketene intermediate formed by loss of HCl from the initial 1,4-addition of amine. Ring closure to give the *trans*-2-azetidinone minimizes steric interactions in the transition state leading to the final product. In these systems, the initial 1,4-addition sets the stereochemistry at both C3 and C4 of the azetidinone ring.



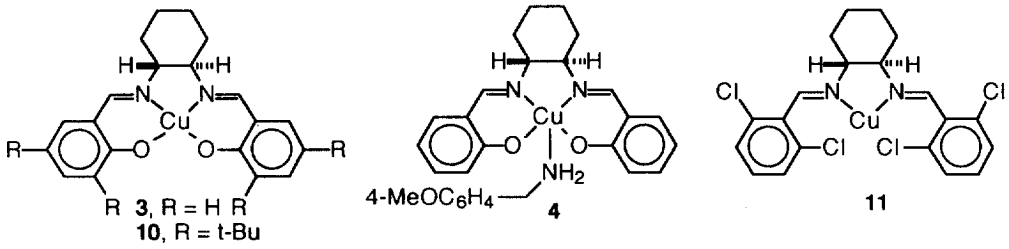
Scheme 1. [3+1] Synthesis of *trans*-3-arylsulfonyl-4-phenyl-2-azetidinones.

The [3+1] route of Scheme 1 increases in practical value if chiral azetidinones **1** can be prepared. Of the two major routes to chiral 2-azetidinones, one achieves enantioselectivity through the use of a chiral auxiliary in the [2+2] cycloaddition of a ketene and an imine[2] and the other uses ring-closure of chiral β-aminoacids.[3] The reaction of Scheme 1 constructs the ring from achiral components that do not readily accommodate a chiral auxilliary. One possible enantioselective route is the addition of chiral amines to acid chlorides **2**. Diastereoselection would set chiral centers at C3 and C4. However, the addition of α-methylbenzylamine to **2** (Ar = Ph) gives only a 68:32 mixture of diastereomers[1] and the amine is consumed as a stoichiometric reagent.

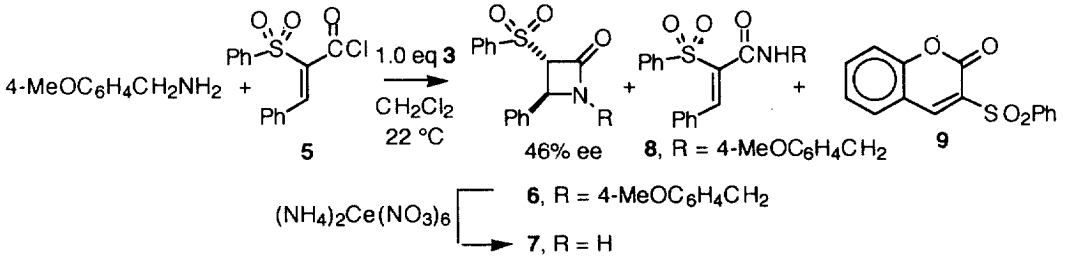
Two approaches for catalytic,asymmetric 1,4-additions have been described that have application to our [3+1] reaction. In one, chiral Lewis acids complex with the carbonyl prior to 1,4-addition to give facial

0040-4039/99/$ - see front matter
PII: S0040-4039(98)02473-3

selectivity during the approach of a non-chiral nucleophile.[4] Propenoyl chlorides **2** offer both sulfonyl and acid chloride functionality as Lewis-acid binding sites. In the other, a chiral catalyst complexes with an achiral nucleophile to give a chiral nucleophilic complex, which might give facial selectivity in the approach to **2**.[5] Copper-complexes of Jacobsen-type ligands were chosen as chiral Lewis acids in order to form tight complexes with the 2-arylsulfonylpropenoyl chloride **2**.[6] Amine complexes of these Lewis acids were also isolable as potential chiral nucleophiles. Partial evaporation of a solution of *p*-methoxybenzylamine and (*R*,*R*)-**3**[7] precipitated the chiral amine complex **4** as green crystals in > 95% yield.[8]



Azetidinone **6**[1] was isolated in 54% yield with a 46% ee[9] of the (-)-enantiomer following the addition of 1 equiv of *p*-methoxybenzylamine to a CH_2Cl_2 solution of 1 equiv of **3** and 1 equiv of Z-3-phenyl-2-(phenylsulfonyl)propenoyl chloride (**5**)[1] (each at 0.1 M, premixed for 5 min) at ambient temperature (Scheme 2). The catalyst **3** was recovered in > 90% yield via trituration of the reaction mixture with hexanes. The Lewis acid was reused in subsequent reactions without loss of enantioselectivity. Small amounts (< 5%) of amide **8**[1] were isolated from the reaction. A new product that was not observed in the uncatalyzed reaction[1] was also isolated in low yield and was identified as coumarin **9**.[8,10]



Scheme 2. Enantioselective synthesis of azetidinone **6** via 1,4-additions.

A single recrystallization of the 46%-ee product from EtOAc-hexane gave enantiomerically pure (-)-**6**[8] (22% overall yield from **5**) with $[\alpha]_D$ = -28.5° (c = 0.8, CH_2Cl_2). The *N*-*p*-methoxybenzyl substituent was oxidatively removed with ceric ammonium nitrate in aqueous acetonitrile[1] to give a 74% yield of enantiomerically pure azetidinone **7** with $[\alpha]_D$ = -19.2° (c = 0.8, CH_2Cl_2).[11] The absolute configuration of (-)-**7** as (3*S*,4*S*) was established by single-crystal, X-ray crystallographic analysis (Figure 1).[12]

The addition of ammonia to acid chloride **5** gives azetidinone **7** directly.[1] However, premixing 1 equiv each of chiral Lewis acid **3** and acid chloride **5** prior to the addition of ammonia at 22 °C gave (-)-**7** in 74% isolated yield but in only 6% ee. In these reactions, less than 5% of amide **8** (R = H) was formed and none of the coumarin **9** was detected.

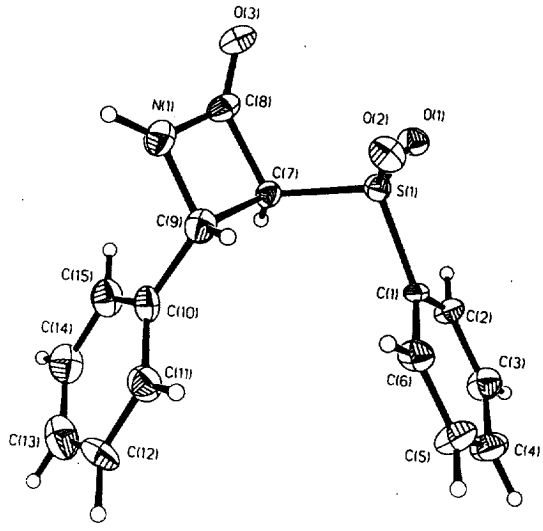


Figure 1: An ORTEP plot of (3*S*,4*S*)-3-phenylsulfonyl-4-phenylazetidin-2-one [(-)-**7**] as determined by single crystal, X-ray crystallographic analysis. Thermal ellipsoids are shown at the 50% probability level.

Although the role of **3** in Scheme 2 was catalytic, the kinetics of the catalyzed and uncatalyzed processes were such that optimal enantioselectivity was observed with stoichiometric **3**, with ee's decreasing to 19% with 0.5 equiv and to 1% with 0.1 equiv of **3**. The use of 2.0 equiv of **3** actually gave a slight decrease in the observed ee (38% ee). The observed ee's of the (-)-enantiomer also decreased as the temperature was lowered giving only 10% ee at -78 °C using 1 equiv of amine, **5**, and **3**.

The enantioselectivity of amine addition was quite sensitive to the structure of the salen ligand. Lewis acid **10**[4b] gave (-)-**6** with 5% ee under conditions identical to those employed with **3** to give (-)-**6** with 46% ee. Imine complex **11**[6] gave essentially racemic **6** (≤ 2% ee) under similar conditions. We surmise that the steric bulk of the *tert*-butyl substituents of **10** hinder complexation of the Lewis acid and/or approach of the nucleophileto the Lewis acid complex. Imine complex **11** lacks the chelating phenolic ligands of **3** and **10** which may limit the rigidity of the Lewis acid complex with **5**.

We also examined the delivery of stoichiometric *p*-methoxybenzylamine and **3** to acid chloride **5** as the complex **4**. The addition of 1.0 equiv of **4** to a CH_2Cl_2 solution of acid chloride **5**[1] at 22 °C gave 2-azetidinone **6** in 54% isolated yield with a 12% ee of the (-)-enantiomer while addition of **4** at -78 °C gave only 7% ee. The addition of ammonia complexes of **3** or **10** to acid chloride **5** gave only racemic **7**. In the reactions of the amine complex **4**, either direct transfer of the amine to **2** or dissociation of amine and **3**, followed by complexation of **3** with **2**, and 1,4-addition of amine can contribute to the 12% ee observed.

Several competing reactions complicate the enantioselective synthesis of Scheme 2. As shown with isolation of complex **4**, the amine can compete with acid chloride **2** for the Lewis acid, which limits the effective concentration of the Lewis acid-**2** complex. Premixing stoichiometric **2** and **3** followed by addition of amine gives azetidinone **6** in 46% ee while addition of amine complex **4** gives only 12% ee. This suggests either that

1,4-addition of amine to the Lewis acid-**2** complex is fast relative to dissociation of the Lewis acid and formation of complex **4** or that the equilibria involved favor the Lewis-acid **2** complex relative to complex **4**.

In summary, chiral Jacobsen-type Lewis acids can be used to catalyze enantioselective 1,4-additions of amines to propenoyl chloride derivatives to give azetidinone products. Little of the competing 1,2-addition of amine to the acid chloride functionality is observed. Although 46% ee was the maximum observed in this study, the use of acid chlorides as carbonyl partners for 1,4-additions of amines and the construction of chiral azetidinones from achiral precursors represent novel observations for further study. We are currently examining other propenoyl chloride derivatives with electron-withdrawing groups at the 2-position as well as other metals with Jacobsen-type ligands and other ligands such as chelating chiral oxazolines.[13]

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8. For **4**: mp 320 °C (dec), **Anal.** Calcd for $C_{28}H_{31}CuN_3O_3$: C, 64.54; H, 6.00; N, 8.06. Found: C, 64.67; H, 6.05; N, 8.00. For (-)-**6**: mp 141-143 °C. For **9**: mp 208-210 °C, ^{1}H NMR ($CDCl_3$) δ 8.81 (s, 1 H), 8.15 (AA'BB', 2 H, *J* ('doublet') = 8 Hz), 7.27-7.73 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 156.2, 155.6, 148.3, 139.1, 136.0, 134.9, 131.1, 130.3, 130.1, 129.8, 129.1, 126.2, 118.0, 117.8, 115.0; IR (KBr) 1742 cm^{-1}; EI MS, *m/z* 286.0283 (Calcd for $C_{15}H_{10}O_4S$: 286.0300).
9. The ee's of **6** were determinedfrom the ^{1}H NMR integrals of the methoxy singlets following the addition of chiral shift reagent {europium tris[3-(heptafluoropropylhydroxymethlene)-(+)-camphorate]}.
10. Compound **9** was not formed from either a mixture of **5** and **3** in the absence of *p*-methoxybenzylamine or from the carboxylic acid of **5** in the presence or absence of *p*-methoxybenzylamine. A plausible source of **9** is exchange of a salicylaldehyde equivalent from **3** with a benzaldehyde equivalent from acid chloride **5** (perhaps involving imine derivatives of *p*-methoxybenzylamine) and cylization to the coumarin.
11. The ee's of **7** were determined by chiral HPLC.
12. Single crystals of (3*S*,4*S*)-(-)-**7** (mp 184-185 °C, $C_{15}H_{13}NO_3S$, M = 391.47) crystallized from EtOAc as colorless needles in the monoclinic space group C2/c, a = 12.0460(2) Å, b = 15.6871(3) Å, c = 15.1252(3) Å, α = 90°, β = 111.6410(10)°, γ = 90°, V = 2656.70(9) Å^3, Z = 8, D_c = 1.437 g cm^{-3}, u = 2.50 cm^{-1}, T = 193 K. Data were collected on a Siemens SMART CCD Area Detector System using Mo Kα (λ = 0.71073) radiation, θ-range 2.23 to 28.24°. Of 8042 reflections measures (±h, ±k, ±l), 3102 were unique and 2873 had $I > 2\sigma$. The structure was solved by direct methods and refined (based on F^2 using all data) by full matrix least-squares methods. Final discrepancy factors: R_1 = 3.41% and $wR2$ = 8.41%. The authors have deposited the atomic coordinates for the crystal structure of (3*S*,4*S*)-**7** with the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U. K.
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