1- Synthesis and Antiviral Activity of 1,3,5-Triazine Derivatives

Several derivatives of 1,3,5-triazine-2-carboxamides 4a-p were synthesized by nucleophilic reactions of the substituted anilines with dicyandiamide in the presence of aqueous HCl to afford 1-arylbiguanide hydrochloride salts la-d. The latter were directly cyclized to 1-aryl-3-(4,5-dioxo-2-imidazolidinylidene) guanidines 2a-d with diethyl oxalate in sodium methoxide solution. Prolonged boiling of compounds 2a-d with water yielded 4-amino-6-arylamino-1,3,5-triazine-2-carboxylic acids 3a-d. Further reaction of the latter compounds with thionyl chloride gave acid chlorides which upon reaction with the appropriate amines afforded the target compounds 4a-p. The newly synthesized compounds were tested for their antiviral activity against HSV-1 and cytotoxicity against Vero cells, compounds 4a and 4b showed marked effect.

2- Kinetic Resolution of 5-Substituted Cycloalkenones by Peptidic Amidophosphane-Copper-Catalyzed Asymmetric Conjugate Addition of Dialkylzinc.

Asymmetric conjugate alkylation reaction of racemic 5-substituted cyclohexenones with dialkylzinc reagents was catalyzed by 2â€“5 mol% of dipeptidic amidophosphane-Cu(MeCN)4BF4 in toluene at 0°C for 20 min to recover enantioenriched starting 5-substituted cyclohexenones with 88â€“98% ee in 28â€“41% yield along with trans major 3-alkylated 5-substituted cyclohexanones with 81â€“90% ee in 53â€“60% yield. Complete consumption of starting racemic 5-TMS-cyclohexenone by treating with diethylzinc under the catalytic asymmetric reaction conditions gave trans major 85:15 mixture of trans- and cis-3-ethyl-5-TMS-cyclohexanones with 15% ee (for trans) in 83% combined yield, indicating that the conformation-controlled trans-alkylation of cyclohexenone prevails over chiral catalyst-controlled enantiofacial differentiation.

3- Peptidic Amidomonophosphane Ligand for Copper-Catalyzed Asymmetric Conjugate Addition of Diorganozincs to Cycloalkenones

Peptidic modification of (S)-2-[(diphenylphosphino)methyl]pyrrolidine gave a dipeptide-connected amidomonophosphane ligand for the highly efficient, copper-catalyzed asymmetric conjugate addition reaction of organozinc reagents with cycloalkenones, giving 3-alkylated cycloalkanones in high enantioreactivity of up to 98 % ee. A model that predicts the stereochemistry of the reaction is discussed.

4- Amidophosphane-Copper(I)-Catalyzed Asymmetric Conjugate Addition of Dialkylzinc Reagents to Racemic 6-Substituted Cyclohexenones to Form 2,5-Di- and 2,2,5-Trisubstituted Cyclohexanones

The asymmetric conjugate addition of dialkylzinc reagents to racemic 6-substituted cyclohexenones under the catalysis of chiral amidophosphane-copper(I) complexes gave a mixture of nearly equal amounts of the corresponding trans- and cis-disubstituted cyclohexanones with extremely high catalyst-controlled enantioselectivity. Epimerization
with 1,8-diaza bicyclo[5.4.0]undec-7-ene (DBU) led to the conversion of these mixtures into the thermodynamically more stable trans-2,5-disubstituted cyclohexanone as the major product with up to 96 % ee in up to 96 % yield. The regio- and stereoselective alkylation of the disubstituted cyclohexanone products via the thermodynamically favored enolate gave 2,2,5-trisubstituted cyclohexanones with a quaternary asymmetric carbon atom in good yield.

5-

Copper-Catalyzed Asymmetric Allylic Substitution with Aryl and Ethyl Grignard Reagents.

Phenyl- and ethyl-magnesium bromides undergo regioselective asymmetric allylic substitution with high enantioselectivity under the catalysis of chiral amidophosphane@copper(I) complexes.

6-

Efficient Chiral N-Heterocyclic Carbene/Copper(I)-Catalyzed Asymmetric Allylic Arylation with Aryl Grignard Reagents

Gamma rules: The title reaction was achieved in a highly regioselective manner using aryl Grignard reagents with monodentate chiral N-heterocyclic carbene-copper(I) catalyst to give diarylvinylmethanes with excellent enantiomeric excess in excellent yield.

7-

Chiral Carbene Approach to Gold-Catalyzed Asymmetric Cyclization of 1,6-Enynes.

Chiral C2-symmetric N-heterocyclic carbenes (NHCs) were tested for their stereocontrolling abilities in gold(I)-catalyzed asymmetric cyclization of 1,6-enynes giving the corresponding cyclopentane derivatives with moderate enantioselectivity of up to 59%.

Graphical abstract

8-

Synthesis, biological evaluation and molecular modeling investigation of some new benzimidazole analogs as antiviral agents.

A set of heterocyclic benzimidazole derivatives bearing 1,3,5-triazine group with different substituents at C-2 and C-5 of the benzimidazole ring have been synthesized and evaluated for their antiviral activities against HSV-1. The structures of these compounds have been established by analytical data, IR spectra, 1H NMR, and mass spectra. Compounds 8a and 8b proved to be the most active antitherpetic agents in this study, at EC50% concentrations of 2.9, 3.4 ?g/ml, respectively. Computational evaluation of the quantum chemical descriptors such as hyDROPhobicity (log P), HOMO & LUMO, and the gap energy, were calculated and correlated with the antiviral activity. The tested compounds showed proper degree of hyDROPhobicity (5). The HOMO-LUMO gap energy values of the tested compounds are comparable with the observed values for the antiviral drug, Acyclovir.

9-

Chiral N-Heterocyclic Carbene@Copper(I)-Catalyzed Asymmetric Allylic Arylation of Aliphatic Allylic Bromides: Steric and Electronic Effects on $^3$-$

Selectivity

Chiral N-heterocyclic carbene ligands were electronically and sterically tuned to improve $\beta$-$\gamma$-selectivity in copper(I)-catalyzed asymmetric allylic arylation of aliphatic allylic bromides with several aryl Grignard reagents. High $\beta$-$\gamma$-selectivity was realized when either the aryl group of the Grignard reagent or the aryl group on the N-substituent of the carbene ligand was electron-deficient or when either the carbene ligand or allylic bromide was bulky. The results indicated that electron deficiency and steric hindrance of the initially formed $\gamma$-allyl copper intermediate enhance the rate of the reductive elimination to give $\beta$-$\gamma$-products as major isomers.

Synthesis and antiviral activity of benzimidazolyl and triazolyl-1,3,5-triazines.

A novel series of 1,3,5-triazine analogs was successfully synthesized through conjugation with benzimidazole or 1,2,4-triazole derivatives via a methylenethio linker. The new analogs were in vitro evaluated against HSV-1 in Vero cells; among these analogs, two compounds exhibited good effect in inhibiting HSV-1 replication (for compound 5p: EC50 = 3.5 lg/ml, SI = 358; for compound 5r: EC50 = 5.0 lg/ml, SI = 300) in comparison to acyclovir.

Rhodium-Catalyzed Reductive Cyclization of 1,6-Enynes and Stereoselective Synthesis of the Putative Structure of Lucentamycin A and its Stereoisomers.

A Rh-catalyzed diastereoselective reductive cyclization, mediated by hydrogen, of optically active 1,6-enynes using chiral BINAP was successfully applied to the total synthesis of four stereoisomers of the proposed structure of lucentamycin A. In order to synthesize two of these four stereoisomers, we successfully constructed chiral proline derivatives bearing cis-carbon substituents at C2 and C3 positions based on Krischeâ€™s methodology, which has very rarely been reported. Anti-proliferative activities on HCT-116 cell line and NMR data of these four stereoisomers were compared with those of naturally occurring lucentamycine A. The results show that the proposed structure of lucentamycin A needs revision.

Steric Tuning of C2-Symmetric Chiral N-Heterocyclic Carbene in Gold-Catalyzed Asymmetric Cyclization of 1,6-Enynes.

Steric tuning of C2-symmetric chiral N-heterocyclic carbene (NHC) was performed in Au(I)-catalyzed asymmetric cyclization of 1,6-enyne. Higher enantioselectivity was realized when chiral
NHCeAuCl/AgSbF6 catalysts whose N-substituent on the NHC overlays the AueCl bond was utilized.

13-

**Stereoselective Total Synthesis of the E-Isomer of Putative Lucentamycin A.**

A synthesis of the E-isomer of the proposed structure of the novel tripeptide, lucentamycin A, was performed in an attempt to define the correct stereochemistry of this natural product. The synthetic route developed employs a stereoselective Rh-catalyzed reductive cyclization process to generate the key pyrrolidine residue in the target and a stereospecific inversion of the Z-olefin geometry to form desired E-isomer. Subsequent amide coupling reactions afforded the desired E-isomer of putative lucentamycin A. A comparison of the NMR data of synthetic E-1a with that of the naturally occurring lucentamycin A demonstrated that they are not identical substances and the E-1a was found to display no anti-proliferative activity on the colon cancer cell line HCT-116 in contrast to natural lucentamycin A.

14-

**Organocatalytic Enantio- and Diastereoselective 1,3-Dipolar Cycloaddition Between Alanine-Derived Ketonitrone and E-Crotonaldehyde: Efficiency and Full Stereochemical Studies.**

Highly enantio- and exo-selective 1,3-dipolar cycloadditions of alanine-derived ketonitrone to E-crotonaldehyde could be realized in a good yield by the use of a chiral imidazolidinone salt without the addition of water. The origin of the stereoselectivity in the reaction was discussed and the absolute configuration of the cycloadduct determined unambiguously.