Asymmetric Catalysis in Intramolecular Cyclopropanation

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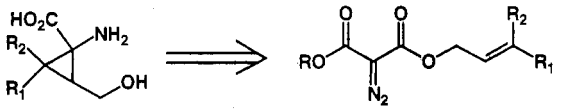
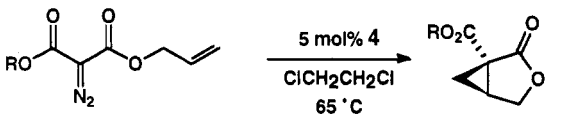
We have recently reported an efficient synthesis of racemic 1-amino-1-cyclopropanecarboxylic acids (ACC's) **1** employing intramolecular cyclopropanation of the precursor allyl diazomalonates **2**.[1] The ACC's have gained considerable synthetic interest,[2] at least in part due to their pronounced conformational and reactivity features in peptide mimics.



1 **2**

Asymmetric catalysis with copper–C_2-symmetric bisoxazoline[3,4] and chiral rhodium[5] catalysts has been favorably utilized in intermolecular cyclopropanation reactions. In intermolecular cases, the problem of *cis–trans* selectivity in the resulting cyclopropanes has been solved only through circuitous routes, most favorably through the use of bulky esters.[4,6] From the ligands' point of view the groups responsible for chirality induction have been grown in size to enhance stereoselectivity. Diazomalonates, however, are known to be sensitive to steric effects in the transition state already in intermolecular reactions, and therefore, the rules derived for intermolecular reactions may not be applicable in this kind of intramolecular reaction.[7] In intramolecular cyclopropanations, significant ee's have been obtained only recently through the use of chiral dirhodium(II) catalysts.[8] Although chiral copper complexes have thus far been able to induce only low to moderate enantioselectivities in intramolecular reactions of diazo(di)carbonyl compounds,[9] copper catalysis is still of great interest because of the inexpensiveness of the catalysts and wide variability of possible types of ligands.[10]

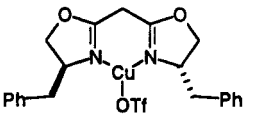
We now wish to report the extension of this methodology to include two important features: (i) use of diazomalonates **2** to facilitate entry into the important ACC's **3**, and (ii) intramolecular cyclopropanation to solve the problem of *cis–trans* relative stereochemistry. This paper describes the first application of this important reaction in the intramolecular cyclopropanation of diazomalonate derivatives.



2a R = Me
2b R = tBu

5 mol% **4**
$ClCH_2CH_2Cl$
65 °C
72–73%

3a R = Me
3b R = tBu



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Both Me and *t*-Bu allyl diazomalonates **2a,b** cyclize efficiently to the corresponding cyclopropanolactones **3a,b** (72–73% isolated yields) upon treatment with the phenylalaninol-derived chiral catalyst **4** under mild conditions. When the diazomalonate is added to the solution of 5–10 mol % of **4** in dichloroethane at room temperature, no reaction or evolution of nitrogen is observed. As the mixture is heated, gas evolution commences at ca. 65 °C, and the formation of the product is rapidly visible on TLC. The reaction with **4** as the catalyst is considerably faster than with $CuI{\cdot}P(OEt)_3$.[1] Control studies on the reaction at several temperatures were also run to establish the effect of the reaction temperature. Below 65 °C, the intermediate carbene complex decomposes very slowly, and prolonged reaction times lead only to increasing amounts of side products. When there was almost no change in reaction rates between 45 and 55 °C, an equal rise of 10° to 65 °C shortened the reaction time to approximately one-third of the time needed for complete comsumption of starting material at lower temperatures. The reaction also seems to be sensitive to even small changes of temperature around 65 °C. A change of only 5 °C was enough to alter the appearance of the product from pale yellow oil, where the color most probably is due to dimerized carbene products, to a white solid containing almost exclusively cyclopropanation product. The use of higher reaction temperatures (e.g., 85 °C) completed the reaction in 3 h, but the enantioselectivity dropped to ca. 15% ee. At 65 °C the

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reaction time for methyl ester was found to be much longer than for *tert*-butyl ester, 46 h vs 6 h. The work on determination of reaction parameters is currently underway.

The optical purity of **3b** was determined by HPLC analysis of the diastereomeric phenethylamine derivative to be 32 (±5) % ee. The sense of absolute stereochemistry is based on optical rotation ($[\alpha]_D$ = +41.5°) and the reported literature value of **3b** ($[\alpha]_D$ = −105.5°).[11] For lactone **3a** the enantiomeric excess was determined by the same method to be 11% ee. The sign of optical rotation of **3a** ($[\alpha]_D$ = +25.2°) is equal to the sign of **3b**, which indicates the same enantiomer in both cases.

The racemic cyclopropanolactone **3b**[12] has been converted to a number of ACC's,[1] and work is currently in progress to incorporate some of these compounds, in enantiopure form, to peptide mimics. Synthetic, conformational, and pharmacological aspects of these mimics will be reported in due course.

Experimental Section

General Procedures. Dichloromethane and 1,2-dichloroethane were refluxed with and distilled from calcium hydride prior to use. Methanol was dried by distilling from magnesium methoxide. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from Merck. HPLC analyses of diastereomeric ratios were performed using a Waters 501 pump with a Waters 440 absorbance detector (λ = 254 nm) and a Merck-Hitachi D-2500 integrator or with a Waters 486 tuneable absorbance detector (λ = 254 nm) and a Waters 746 integrator. Copper(I) triflate was prepared according to literature procedure.[13] (4*S*,4′*S*)-4,4′,5,5′-Tetrahydro-2,2′-methylene-4,4′-dibenzylbisoxazole was prepared in one step from dimethyl malonate and L-phenylalaninol according to a method by Lowenthal et al.[3a] Diazomalonates **2** were prepared according to a method published earlier.[1,14] Melting points were determined on a Kofler-type hot plate apparatus. Optical rotations were determined on a Perkin-Elmer 243B digital polarimeter in a 1 dm/1mL cell.

(1*S*,5*S*)-(+)-1-(*tert*-Butoxycarbonyl)-2-oxo-3-oxabicyclo-[3.1.0]hexane (3b). A solution of **2b** (122 mg, 0.54 mmol) in 2 mL of 1,2-dichloroethane was added via syringe to a solution of the catalyst **4** (15 mg, 0.027 mmol) in 1 mL of 1,2-dichloroethane under an argon atmosphere. The mixture was brought to 65 °C (after a short period of time the solution started to effervesce and turned faintly brown in color) and kept at that temperature until the starting material was consumed by TLC analysis (1:4 EtOAc/hexane, UV, R_f = 0.46). The reaction mixture was then cooled to room temperature and evaporated to dryness in vacuo. Kugelrohr distillation gave the product **3b** as a viscous colorless oil, which solidified on standing (78 mg, 73%): mp 72–74 °C (lit.[1] mp 73–74 °C), $[\alpha]_D$ = +41.5°, for the enantiomer of **3b**, (lit.[11] $[\alpha]_D$ = =105.5° (*c* = 1.3, CH_2Cl_2). The ^1H NMR and ^{13}C NMR spectra were identical to those of authentic material.[1]

(1*R*,5*S*)-(+)-1-(Methoxycarbonyl)-2-oxo-3-oxabicyclo[3.1.0]-hexane (3a) was prepared in a similar fashion from **2a**,[1] with a yield of 72%; mp 68–70 °C, (lit.[15] mp 46–47 °C), $[\alpha]_D$ = +25.2°. The ^1H NMR and ^{13}C NMR spectra were identical to those of authentic material.[1]

Determination of Enantiomeric Excess. Lactone **3b** (19.8 mg, 0.1 mmol) was dissolved in 50 μL of dry methanol, and D-(+)-α-phenylethylamine (12.1 mg, 0.1 mmol) was added. The solution was heated at 50 °C for 22–36 h and then cooled to room temperature. The resulting mixture was dissolved in 0.5 mL of dichloromethane, washed with 5% citric acid and brine, and finally dried with $MgSO_4$. After filtration, the solution was evaporated to dryness with a flow of nitrogen and redissolved to the HPLC solvent. The diastereomer ratios were determined by HPLC (Shandon Hypersil 5-μm column, 20% EtOAc in isooctane as eluent, flow rate 3.0 mL/min). Enantiopurity of lactone **3a** was determined by an equal method, except that 5-fold excess of phenethylamine was used.

Preparation of the Catalyst 4. (4*S*,4*S*′)-4,4′,5,5′-Tetrahydro-2,2′-methylene-4,4′-dibenzylbisoxazole (227 mg, 0.9 mmol) was dissolved in 10 mL of dichloromethane under argon and added via syringe to a flask containing CuOTf-0.5-PhH (276 mg, 0.9 mmol) under argon atmosphere. The solution was stirred overnight and the solvent evaporated with a gentle flow of argon to give the complex as a slightly greenish solid, which was found to be air stable for an undetermined time. The catalytic activity of this complex was established by intermolecular cyclopropanation of various olefins with ethyl diazoacetate, giving good results in good accordance with literature.[3]

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