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INTERMOLECULAR CYCLOPROPANATION VERSUS C-H INSERTION IN METALLOPHTHALOCYANINE-CATALYZED CARBENOID REACTIONS WITH CYCLOHEXENE

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Abstract

Transition metal-catalyzed decomposition of diazo compounds in the presence of cyclohexene results in a product ratio of cyclopropanation and intermolecular C-H insertion. The ratio of these products is highly dependent on the type of metal catalyst used and on the substituents of the diazo compound. This study examined the chemoselective control of cyclopropanation and C-H insertion in the decomposition of methylphenyldiazoacetate using metallophthalocyanine complexes as catalysts. Controlling the selectivity of the products formed from these reactions could be useful for synthesis of complex organic structures. These reactions proceed in a relatively short period of time and produce good yields. In particular, CuPc demonstrated to be the most selective, favoring cyclopropanation at a ratio of 6.4:1.

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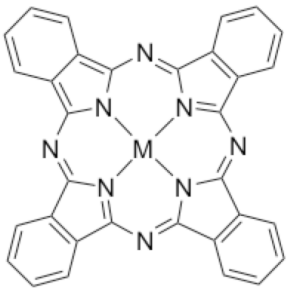
Introduction

Metallophthalocyanines (MPc) are large aromatic macrocyclic molecules with a metal at their core (Figure 1). They are often used in industrial pigments.[1,2,3] More recently they have been explored as catalysts in organic transformations including carbenoid reactions such as cyclopropanation and olefination.[4,5] Studies examining the potential contribution of MPcs in these carbenoid reactions has been relatively limited.[4] These metal-carbenoid reactions are highly dependent on the structure and electrophilicity of the carbenoid.[6] An electrophilic carbenoid will result in reactions with low selectivity.[4] Selectivity can be enhanced, and side reactions can be minimized by functionalizing the carbenoid with electron donating and electron accepting groups.[7] Selectivity has also been enhanced by using donor-acceptor diazo compounds.[8] Other metal complexes have been examined to catalyze these reactions such as rhodium, silver, gold, and copper complexes. Chiral Rh II catalysts have been shown to favor allylic C-H insertion over cyclopropanation.[9] Müller and coworkers have shown in experiments using Rh II catalysts with cyclohexene and methyl phenyldiazoacetate as reagents, total yields of C-H insertion and cyclopropanation products were acceptable, ranging from 33-52%, with the highest selectivity observed in methyl phenyldiazoacetate at a ratio of 93:7.[9] In contrast, Ag, Cu, and Au complexes have been shown to favor cyclopropanation over C-H insertion.[10] A particular study by Thompson and Davies compared $AgSbF_6$ and Rh II acetate catalyzed reactions of cyclohexene and found $AgSbF_6$ strongly favored cyclopropanation at a ratio of >15:1 and was produced at a high total yield of 88%, while Rh II catalyst favored C-H insertion at a ratio of 2.2:1 with an acceptable total yield of 44%.[11] The research herein sought to investigate chemoselective control of intermolecular cyclopropanation versus C-H insertion using metallophthalocyanines as catalysts in donor/acceptor carbenoid reactions with cyclohexene.

Figure 1. Structure of Metallophthalocyanine (MPc)



M = Ag, Co, Cu, Fe, Mn, Ni, Zn

Experimental Methods

General Information:

All reactions were conducted in oven or flame-dried glassware under an inert atmosphere of dry argon. All reagents were used as received from Sigma-Aldrich unless otherwise stated. Flash chromatography was performed on silica gel (32-63D 60 Å) according to the method of W. C. Still.[12] Thin layer chromatography (TLC) was performed on aluminum backed plates pre-coated with silica (0.25 mm, 60F-254) which were developed using standard visualizing agents: UV fluorescence (254 and 366 nm). ^{1}H NMR spectra were recorded on a Nuclear Magnetic Resonance spectrometer at 400 MHz calibrated by using residual undeuterated tetramethylsilane (TMS) solvent as an internal standard. The following abbreviations apply: (s) singlet, (d) doublet, and (m), multiplet. Chemical shifts are given in ppm. J-values are recorded in Hz and are rounded to the nearest tenth. Product ratios were determined by from ^{1}H NMR spectra of the crude reaction mixture.

Starting Materials:

All of the starting materials were purchased from Sigma-Aldrich or Acros and used as received. **Methyl phenyldiazoacetate (2)** was synthesized and used as described in the literature.[12] 1,8-Diazabicyclo(5.4.0)undec-7-ene (1.14 g, 8.16 mmol, 1.1 equiv.) was added to a solution of methyl phenylacetate (1.02 g, 6.80 mmol, 1.0 equiv.) and *para*-acetobenzenesulfonyl azide (1.14 g, 7.48 mmol, 1.2 equiv.) in 25 mL of acetonitrile at 0°C. The resulting solution was stirred for 3 hours. Then quenched with 50 mL of saturated NH_4Cl solution and extracted with EtOAc (3 x 25 mL). The combined extracts were dried with Na_2SO_4 and filtered. The residue was concentrated *in vacuo* and purified by flash chromatography on silica gel using 5% ether/hexanes to furnish the product as an orange oil, 0.8979 g (75%). ^{1}H NMR (400 MHz) δ 7.47 (d, J = 8.8 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 3.87 (s, 3H). The spectroscopic data is consistent with previously reported data.[13]

General Procedure

In a dried round bottom flask, the catalyst, metallophthalocyanine (MPc), was added directly into the flask (0.01 mmol, 1 mol %) along with cyclohexene, **1** (0.821 g, 10.0 mmol, 10 equiv.) to 5 mL of anhydrous α,α,α-trifluorotoluene ($PhCF_3$) (Table 1). The entire solution was degassed with argon and heated to reflux under argon. The methyl phenyldiazoacetate, **2** (0.176 g, 1.0 mmol, 1 equiv.) was dissolved in 5 mL of degassed, anhydrous α,α,α-trifluorotoluene and added to the reaction dropwise over 2 hours via syringe pump. The resulting solution was allowed to stir at reflux overnight (12 hours) after addition was completed and then concentrated in vacuo. The crude material was analyzed by ^{1}H NMR spectroscopy. The resulting residue was purified by flash chromatography on silica gel using 25:1 hexanes/diethyl ether as eluent to isolate the corresponding products **3** and **4**.

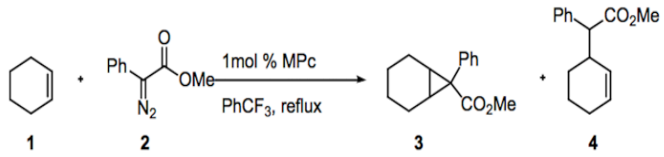
Cyclopropane **(3)**, **Methyl 7-phenylbicyclo[4.1.0]heptan-7-carboxylate**, was isolated as a white solid. R_f= 0.64 (20% diethyl ether/hexanes). ^{1}H NMR (400 MHz) d 7.38-7.26 (m, 5H), 3.54 (s, 3H), 2.01-1.94 (m, 4H), 1.76-1.69 (m, 2H), 1.08-1.03 (m, 2H), 0.60-0.57 (m, 2H). The spectroscopic data is consistent with previously reported data.[9,11] HRMS (ESI) Calcd for $C_{15}H_{18}NaO_2$: 253.119901. Found: 253.119883.

Olefin **(4)**, **Methyl 2-(cyclohex-2-enyl)-2-phenylacetate**, was isolated as a clear oil (1:1 mixture of diastereomers). R_f= 0.76 (20% diethyl ether/hexanes). ^{1}H NMR (400 MHz) d 7.33-7.26 (m, 5H), 5.78-5.77 (m, 1H, DS1), 5.65-5.62 (m, 1H), 5.17-5.14 (m, 1H, DS2), 3.66 (s, 3H), 3.32 (d, J = 11.2 Hz, 1H), 2.88-2.85 (m, 1H), 2.00-1.04 (m, 6H). The spectroscopic data is consistent with previously reported data.[9,11] HRMS (ESI) Calcd for $C_{15}H_{18}NaO_2$: 253.119901. Found: 253.120298.

Results and Discussion

Seven metallophthalocyanines with different transition metal cores were used to investigate the ratio of intermolecular cyclopropanation and C-H insertion upon reaction with cyclohexene and the donor-acceptor diazo, methylphenyldiazoacetate, 2 (Table 1). The product ratios for all entries, except entry 3, displayed similar chemoselectivities at a nearly 1:1 ratio. An additional comparative experiment was also performed without a catalyst, where the ratio of C-H insertion to cyclopropanation was nearly 1:1, demonstrating that this reaction in the absence of a catalyst did not result in good chemoselective control and was not significantly different from entries 1, 2, 4, 5, 6, 7.Entry 3, which used copper phthalocyanine (CuPc), produced more than six times the amount of cyclopropane, 3, compared to olefin, 4, at 86% total yield.

Table 1: C-H Insertion Versus Cyclopropanation With Cyclohexene as the Substrate



entry	MPc	Ratio **3** : **4**	Yield (%)
1	AgPc	1.3 : 1	80
2	CoPc	1.3 : 1	56
3	CuPc	6.4 : 1	86
4	FePc	1.3 : 1	75
5	MnPc	1.2 : 1	57
6	NiPc	1.1 : 1	83
7	ZnPc	1.3 : 1	64
8	no catalyst	1.3 : 1	68

Conclusions

In conclusion, this study demonstrated that various MPc's can effectively catalyze cyclopropanation and C-H insertion reaction from diazo decomposition. This enhanced selectivity with CuPc has been observed before in cyclopropanation of various styrenes (up to 20:1 ratio of diastereomers) as well as olefination of aldehydes producing cis- or trans- products (>20:1 ratio of stereoisomers).[4,5] The reaction lacking a catalyst furnished products with similar ratios to the reactions with MPcs other than CuPc. Future work will further investigate the thermal decomposition of the diazo compound in these reactions as well as reaction times and temperature to fully investigate the effect of the catalysts in these reactions. Recently, thermal decomposition of diazo compounds has been reported.[5,14] Other future work will further examine the effects of CuPc on reagents with alternate electronics, including varied cycloalkenes and diazo compounds with different donating and withdrawing groups.

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