Brønsted acid-promoted olefin anti-dihydroxylation

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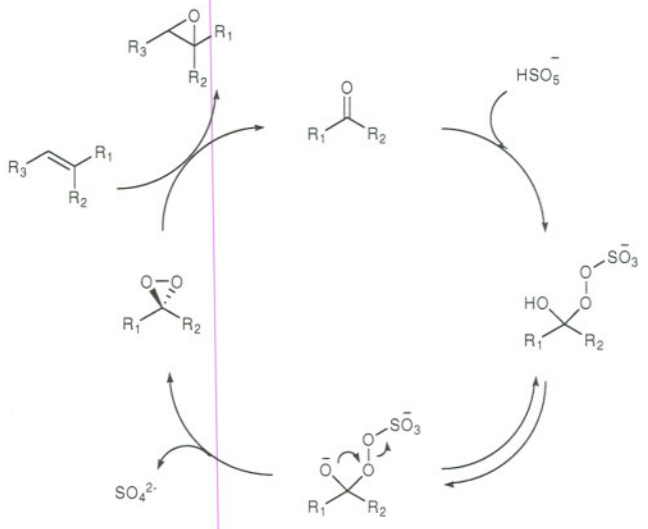
Introduction

The development of asymmetric reaction methodologies continues to provide a convenient means to synthesize chiral, nonracemic organic compounds. For example, asymmetric oxidation reactions such as epoxidation,[1] aziridination, dihydroxylation and aminohydroxylation have been developed and widely applied in organic synthesis.[2] The products of these reactions are often further elaborated by reaction with various nucleophiles. For example, amine can be reacted with chiral epoxides stereospecifically to give chiral *vicinal*-aminoalcohols.

During the past few years, various epoxidation and dihydroxylation methods have been studied and developed by a number of groups. The use of chiral ketones in epoxidation reactions was first investigated by Curci in 1984, and was followed by numerous other chiral ketone catalysts. For example, Shi and co-workers carried out asymmetric epoxidations of olefins by using carbohydrate based chiral ketones.

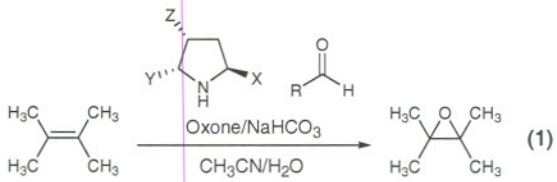
Scheme 1. Mechanism for epoxidation of olefins by chiral ketone and oxone



[1] Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; *Comprehensive Asymmetric Catalysis*; Springer-Verlag, Berlin, 1999.
[2] Lin, Li, Chan. *Principles and Application of Asymmetric Synthesis*; Wiley: New York, 2001.

The mechanism of these reagents proceeds through a dioxirane intermediate, generated in situ from chiral ketones and oxone which carries out the enantioselective epoxidation of olefins (Scheme 1).[3]

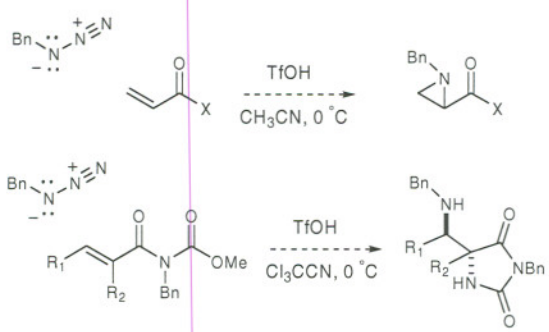
Yang and co-workers have recently developed an enantioselective epoxidation reaction catalyzed by chiral iminium salts that react with oxone. In this reaction, the iminium salts form oxaziridinium salts that act as an oxygen transfer agent (eq 1).[4]



(1)

Recently, the Johnston group has developed the Brønsted acid-promoted aziridination and amino-hydroxylation reaction (Scheme 2).[5]

Scheme 2. Brøsted acid-promoted olefin aminohydroxylation



These reactions are believed to be Brønsted acid promoted Michael additions of azide to the olefin. Similar to these reactions, we wish to examine the Michael addition of ozone to electron deficient olefins to form epoxides. The oxidation reaction of olefin with ozone normally produces a carbonyl by oxidative cleavage of the carbon-carbon double bond. However, there are examples of epoxide formation during ozonation of highly

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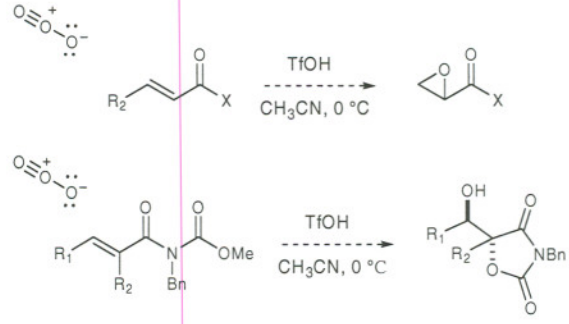
[3] Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488-496.
[4] Wong, M. K.; Ho, L. M.; Zheng, Y. S.; Ho, C. Y.; Yang, D. *Org. Lett.* **2001**, *3*, 2587-2590.
[5] Mahoney, J. M.; Smith, C. R.; Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354-1355.

sterically hindered olefins.[6] We propose the specific use of electron deficient olefins that can be further activated by Lewis acid complexation. The role of the Lewis acid is two fold, a) render the olefin acceptor more electrophilic toward a nucleophile ozone oxygen, and b) slow the rate of malozonide formation leading to carbon-carbon bond cleavage. A variation will include an overall *anti*-dihydroxylation reaction (Scheme 3).

Scheme 3. Brønsted acid-promoted olefin dihydroxylation



Background

The ozonization of a carbon-carbon double bond proceeds via the Criegee mechanism.[7] However, epoxidation and other "partial cleavage" reactions are known to compete reaction with ozonolysis during the oxidation of olefins. In many cases, this competitive reaction depends on the substrate steric and electronic effects, and epoxides can be formed (Scheme 4).[8] The initial species, has been suggested to be [2+1] cycloaddition an ozone-olefin π complex, analogous to cyclic halonium ions. Not surprisingly, steric bulk around the olefin, favors the end-on approach of ozone to the σ complex, resulting in an epoxide.

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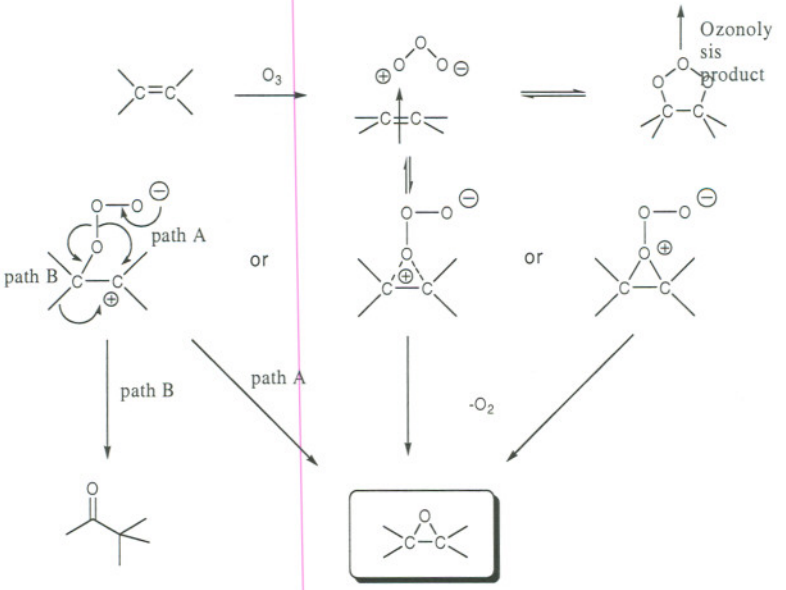
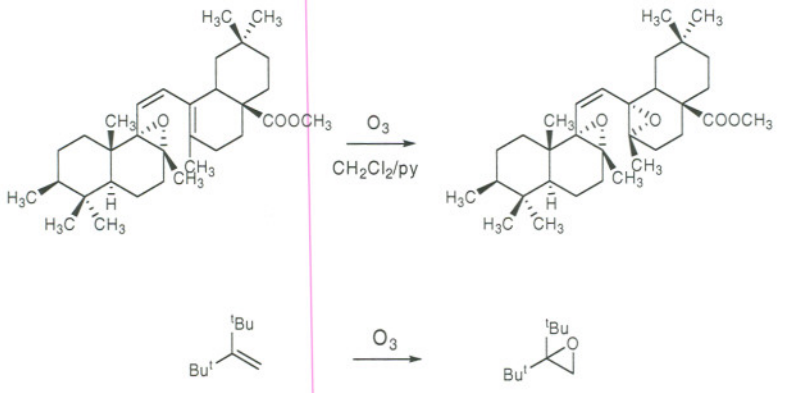
[6] Bailey, P. S. Lane, A. G. *J. Am. Chem. Soc.* **1967**, 89, 4473-4479.
[7] Criegee, R.; *Peroxide Reaction Mechanisms*; Wiley-Interscience: New York, 1962.
[8] Bailey, P. S; Hwang, H. H,; Chiang. *J. Org. Chem.* **1985**, 50, 231-234.

Scheme 4. Mechanism of epoxidation during ozonation



Two examples of olefin epoxidation using ozone are shown in Scheme 6.

Scheme 5. Olefin epoxidation by ozone



We approached the epoxidation using ozone differently and our design requires an unhindered, electron deficient olefin in direct contrast to the examples in Scheme 5.[9]

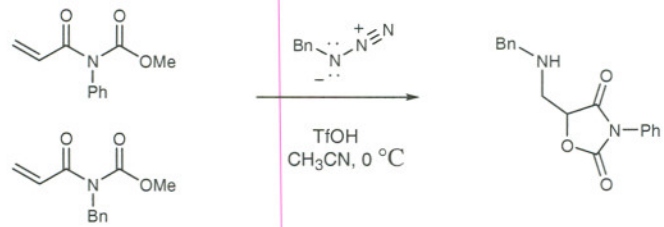
[9] Bailey, P. S; Hwang, H. H,; Chiang. C. Y. *J. Org. Chem.* **1985**, 50, 231-234.

Results and Discussion

We are now developing Bronsted acid catalyzed dihydroxylation reaction based on mechanistic considerations of our previous work. The reaction of electron deficient unsaturated carbamates with benzylazide in the presence of a catalytic amount of triflic acid provides a *trans*-selective amino hydroxylation reaction.[10] Thus, if ozone is used in place of axide in this reaction, then we anticipate that the *anti*-selective dihydroxylated product would form.

While amino-hydroxylation reaction was normally straightforward with N-benzyl carbamates, we projected the need for a more electron deficient olefins since ozone's nucleophilicity is less than the electron rich azide. A competition experiment revealed that *N*-phenyl carbamate (1) is 2.5 more reactive than *N*-benzyl protected olefin.

Scheme 6. Competition reaction of brønsted acid promoted olefin anti-aminohydroxylation



In an attempt to understand the ozone mediated epoxidations and dihydroxylation, and also try to understand our reaction system's nature, the reaction with acryloyl carbamate and ozone was investigated as a standard reaction. First, a solvent screen with normal open system was carried out to evaluate the affect solvent has on the reaction.

Reactions run open to the atmosphere proceeded cleanly to the ozonolysis product. In some cases, several products were also detected, whose identities were not determined.

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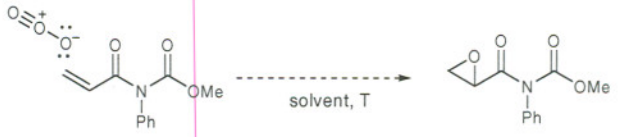
[10] Mahoney, J. M.; Smith, C. R.; Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354-1355.

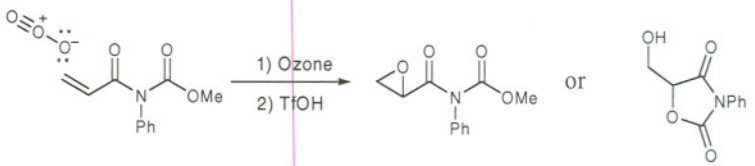
Table 1. Epoxidation attempts with ozone



entry	solvent	Temp (°C)	TfOH (eq)	Product
1	CH_2Cl_2	-78	none	hydrolysis
2	CH_3CH_2CN	-78	2	unknown
3	CH_3CN	-20	2	aldehyde
4	pentane/CH_2Cl_2/py	-20	none	unknown

We hypothesized that atmospheric moisture promoted hydrolysis and the oxidation by ozone. Therefore, we constructed a system for executing these reactions with exclusion of atmospheric moisture. This failed to improve our original findings. We concluded that our first trial which was normal ozone bubbling and then followed by adding triflic acid condition was not enough to promote the desired reaction.

Table 2. Epoxidation and Dihydroxylation Screen



entry	solvent	T (°C)	TfOH (eq)	Product
1	CH_2Cl_2	-20	2	hydrolysis
2	CH_2Cl_2	-78	2	aldehyde
3	CH_2Cl_2	-78	5	aldehyde

We then considered that adding triflic acid first would be more. However, all others gave at best no reaction with many giving messy crude reaction mixtures. Additionally, it should be noted that the starting carbamate was consumed during the reaction (Table 3).

Scheme 7. Proposed Mechanism for Acid-Catalyzed Epoxidation/Dihydroxylation

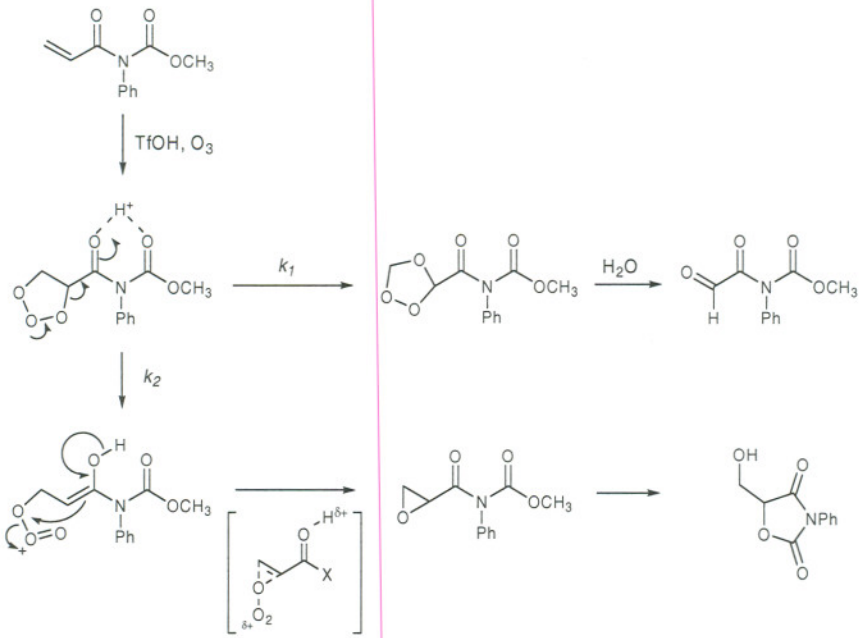
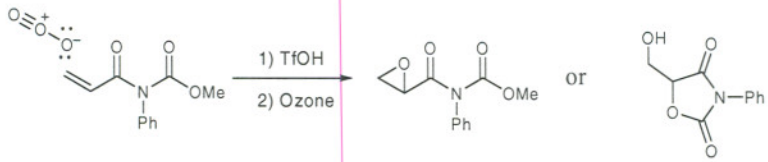


Table 3. Epoxidation and Dihydroxylation Screen 2



entry	solvent	T(°C)	TfOH (eq)	additive	product
1	CH_2Cl_2	-78 ~ -20	2	none	unknown
2	CH_2Cl_2	-78 ~ -20	10	none	not react
3	pentane/CH_2Cl_2/py	-78	2	2 eq $SnCl_4$	unknown
4	pentane/CH_2Cl_2/py	-20	2	2 eq $NH(SO_2CF_3)_2$	aldehyde
5	pentane/CH_2Cl_2/py	-20	2	none	hydrolysis
6	TFA	-78	none	none	plasticizer
7	Et_2O	-78	2	none	unknown
8	MeOH	-78	2	none	unknown
9	MeOH	-78	2	H,Quin,BAM	unknown

Solvents and amount of triflic acid, and the use of an additive effect were screened for their potential to effect the desired epoxidation. Several different solvent systems were

examined (Table 3) as was temperature variation during the ozonolysis and the quantity of triflic acid. However, these were ineffective in promoting epoxidation. Our current hypothesis is that the electron deficient nature of ozone may first need to be overcome before epoxidation is successful.

Conclusion

We have examined the epoxidation and dihydroxylation of electron deficient olefins using O_3/TfOH. Although we have not yet been successful, we expect that further refinements to the reaction conditions will ultimately afford the desired dihydroxylation products.

Experimentals

Flame-dried (under vacuum) glassware was used for all reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. Diethyl ether (Et_2O), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and benzene (C_6H_6) were dried by passage through a column of activated alumina as described by Grubbs.[11] Benzene was additionally passed through a column containing activated Q-5 reactant. Methanol was distilled from Mg under N_2 immediately before use.

Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates and flash chromatography utilized 230–400 mesh silica gel from Scientific Adsorbents. UV light, and/or the use of ceric ammonium molybdate and potassium iodoplatinate solutions to visualize products.

IR spectra were recorded on a Nicolet Avatar 360 spectrophotometer and are reported in wavenumbers (cm^{-1}). Liquids and oils were analyzed as neat films on a NaCl plate (transmission), whereas solids were applied to a diamond plate (ATR). Nuclear magnetic resonance spectra (NMR) were acquired on either a Varian INOVA-400 (400 MHz) or VXR-400 (400 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.1 ($CDCl_3$) and δ 7.15 and δ 128.1 (d_6-benzene). Mass spectra were recorded on a Kratos MS-80 spectrometer by use of chemical ionization (CI). Atlantic Microlabs, GA, performed combustion analyses.

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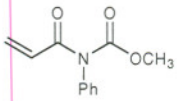
[11] Pangborn, A. B.; Giardello, M.A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520

General Procedure for Lithiation of Amides.

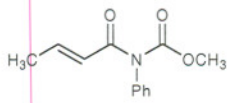
To a round bottom flask, the amide (1.00 eq) and THF were added to give a 0.20 M solution. This was cooled to –78 ºC and 2.5 M butyl lithium (1.05 eq) in hexanes was added dropwise. This was allowed to stir for 10 minutes and the alkyl chloroformate (1.10 eq) was added dropwise. This was allowed to warm over 6 h while stirring. The reaction was quenched with water, diluted in ethyl acetate, separated, and the water layer back extracted. The organic layers were combined, washed with brine, dried, and solvent removed. The residue was then purified using flash chromatography to give the acylated amide.



Acryloyl-phenyl-carbamic acid methyl ester (1)

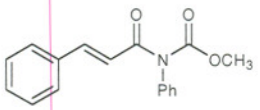
To a round bottom flask, the amide (2.0g, 9.7 mmol, 1.00 eq) and THF (48 mL) were added to give a 0.20 M solution. This was cooled to –78 ºC and 2.5 M butyl lithium (4.07mL, 10.18 mmol, 1.05 eq) in hexanes was added dropwise. This was allowed to stir for 10 minutes and the alkyl chloroformate (0.84 mL, 10.67mmol, 1.10 eq) was added dropwise. This was allowed to warm over 6 h while stirring. The reaction was quenched with water, diluted in ethyl acetate, separated, and the water layer back extracted. The organic layers were combined, washed with brine, dried, and solvent removed. The residue was then purified using flash chromatography to give the acylated amide as white solid (1.69g, 85%). R_f = 0.7 (20% EtOAc/hexanes); IR (film) 3065, 3033, 2957, 1734, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (m, 3H), 7.13-7.11 (m, 2H), 7.03 (dd, J = 16.8, 10.4 Hz, 1H), 6.42 (dd, J = 16.8, 1.2 Hz, 1H), 5.75 (dd, J = 10.4, 1.2 Hz, 1H),

3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 154.7, 138.1, 130.4, 130.2, 129.4, 128.5, 54.1.



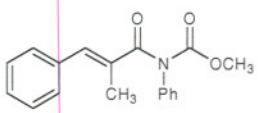
But-2-enoyl-phenyl-carbamic acid methyl ester (2)

White solid (72%). R_f = 0.7 (20% EtOAc/hexanes); IR (film) 3027, 2967, 1733, 1699, 1695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 3H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.04 (dd, *J* = 15.2, 7.2 Hz, 1H), 6.77 (dd, *J* = 15.2, 1H), 3.66 (s, 3H), 1.86 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 154.8, 145.2, 138.4, 129.3, 128.5, 128.3, 124.8, 53.9, 18.5.



Phenyl-(3-phenyl-acryloyl)-carbamic acid methyl ester (3)

White solid (60%). R_f = 0.48 (30% EtOAc/hexanes); IR (film) 3115, 3066, 2957, 1739, 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 15.6 Hz, 1H), 7.55-7.53 (m, 3H), 7.44-7.35 (m, 6H), 7.19 (d, *J* = 7.6 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 154.9, 145.2, 138.5, 135.0, 130.5, 129.4, 129.1, 128.7, 128.6, 128.5, 120.4, 54.1.



(2-Methyl-3-phenyl-acryloyl)-phenyl-carbamic acid methyl ester (4)

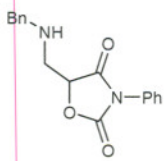
White solid (85%). R_f = 0.51 (30% EtOAc/hexanes); IR (film) 3360, 3060, 3029, 2955, 1739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.30 (m, 10H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.14 (s, 1H), 3.75 (s, 3H), 2.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 155.2, 138.7, 135.8, 134.9, 134.6, 129.6, 129.5, 128.6, 128.4, 128.2, 127.9, 54.1, 15.6.

General Procedure for Acid catalyzed Dihydroxylation

To a vial, the Michael acceptor (1.0 eq) was added with solvent to give 0.3 M solution. This was cooled to –20 °C and triflic acid (2.0 eq) was added. To this, ozone was added and allowed to stir until reaction was complete. The reaction was then diluted in ethyl acetate (10 mL) and washed with 1M NaOH (1 mL). This was dried and purified using flash chromatography to yield the epoxide.

General Procedure for Acid catalyzed Anti-Aminohydroxylation

To a vial, the Michael acceptor (1.0 eq) was added with solvent to give 0.3 M solution. This was cooled to –20 °C and triflic acid (2.0 eq) was added. To this, benzyl azide (2.0 eq) was added and allowed to stir until reaction was complete. The reaction was then diluted in ethyl acetate (10 mL) and washed with 1M NaOH (1 mL). This was dried and purified using flash chromatography to yield the product.



5-(Benzylamino-methyl)-3-phenyl-oxazolidine-2,4-dione (5)

To a vial, the Michael acceptor (50mg, 0.24mmol, 1.0 eq) was added with solvent to give 0.3 M solution. This was cooled to –20 °C and triflic acid (42µL, 0.48mmol, 2.0 eq) was added. To this, benzyl azide (38.5µL, 0.29mmol, 1.2 eq) was added and allowed to stir until reaction was complete. The reaction was then diluted in ethyl acetate (10 mL) and washed with 1M NaOH (1 mL). This was dried and purified using flash chromatography to yield the product as colorless oil (47mg, 68%). R_f = 0.45 (20% EtOAc/hexanes); IR (film) 3348, 3064, 2360, 1822, 1752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.40 (m, 5H), 7.32-7.23 (m, 5H), 4.94 (t, *J* = 3.2 Hz, 1H), 3.83 (d, *J* = 3.2 Hz, 2H), 3.28 (dd, *J* = 13.8, 3.2 Hz, 1H), 3.18 (dd, *J* = 13.8, 3.2 Hz, 1H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 154.6, 139.6, 131.1, 129.5, 129.1, 128.9, 128.7, 128.2, 127.5, 125.9, 54.1, 48.1.