Lithiation of Benzyl Imidazoles and Their Addition to Select Electrophiles: Exploration of Reactivity and Diastereoselectivity.

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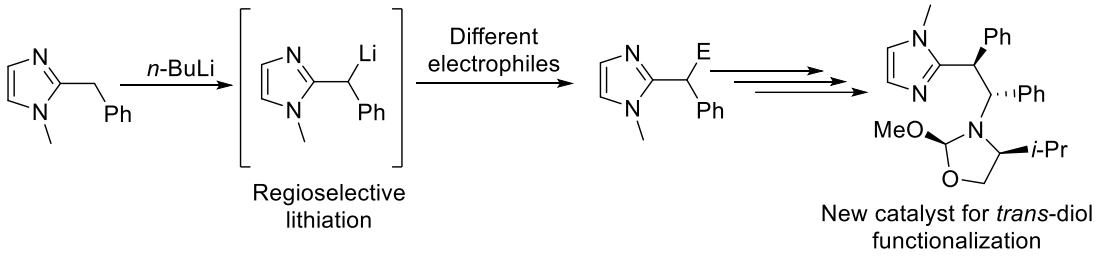
ABSTRACT

Benzyl imidazole was successfully lithiated using n-BuLi at -78°C and verified by deuterium incorporation. The chemical reaction of the lithiated benzimidazole was explored with a series of different electrophiles. This approach was utilized to synthesize new *anti* and *syn* diphenyl organocatalysts for *trans* diol functionalization.

Keywords: benzimidazole, lithiation, organocatalysis, diol fuctionalization

Graphical Abstract



Introduction

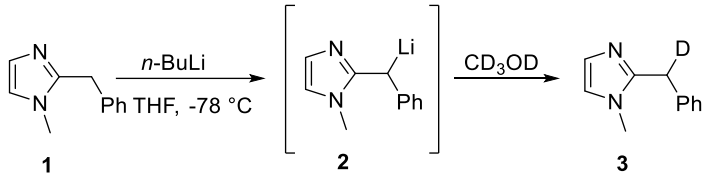
Imidazole derivatives are significant compounds that possess a wide array of biological activities such as antibacterial[1,2] , anti-inflammatory and analgesic [3,4], anti tubercular[5], anti-depressant[5], anti-cancer[6,7] and anti-viral activity.[8] In addition, these scaffolds have been shown to have application in organocatalysis by Tan and co-workers for the desymmetrization *cis* 1,2-diols,[9–11] which is an attractive approach over the traditional methods for mono protection of diols.[12–14] where in Tan's catalyst system, an *aza*-orthoformate moiety acts as substrate binding site tethered to the imidazole moiety which act as a base for deprotonation.

A variety of synthetic approaches have been developed to access biological and/or catalytically relevant imidazole compounds – including lithiation of the benzylic position of the imidazole moiety.[15–17] Herein, we report the selective lithiation of 1-methyl-2-benzyl imidazole and its subsequent reactivity with bezaldehyde and an Elmann chiral sulfinimine for the purpose of generating new catalysts for selective functionalization of *trans* 1,2-diols using scaffold catalysis.[9]

Results and Discussion

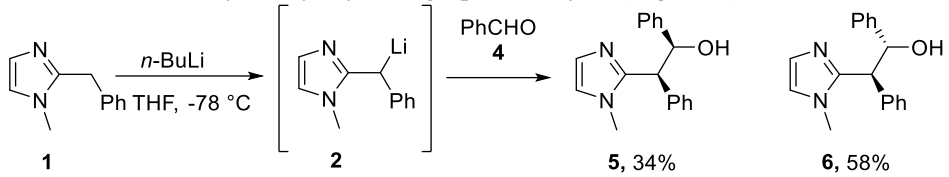
We first set out to confirm the effectiveness of selective lithiation on our key substrate 1

(Scheme 1). Lithiation of 1-methyl-2-benzyl imidazole[18] (**1**) was achieved by using *n*-BuLi as a base at -78°C. The lithiated complex **2** was quenched with CD_3OD to confirm the lithation exclusively takes place at the benzylic methylene in compound **3** without having any reaction at C-5 position. In this study, 87% deuterium incorporation was observed as measured by integration of the residual benzyl protons in the ^1H NMR spectrum.



Scheme 1. Regioselective lithiation of (1) and deuterium incorporation product (3).

To explore the electrophilic addition to the generated lithium complex **2**, benzaldehyde (**4**) was added at -78°C allowing to warm gradually to room temperature (Scheme 2). The reaction proceeded diastereoselectively to give the *syn* alcohol **5** and *anti* alcohol **6** products as the minor and major stereoisomers respectively. The relative stereochemistries of both **5** and **6** were determined by X-ray crystallographic analysis (Figure 1).



Scheme 2. Addition of benzaldehyde to lithiated complex **2**.

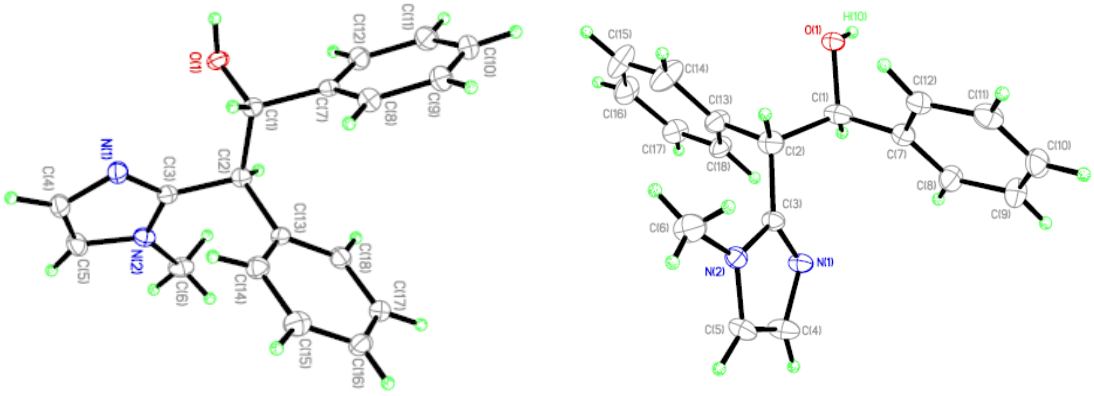
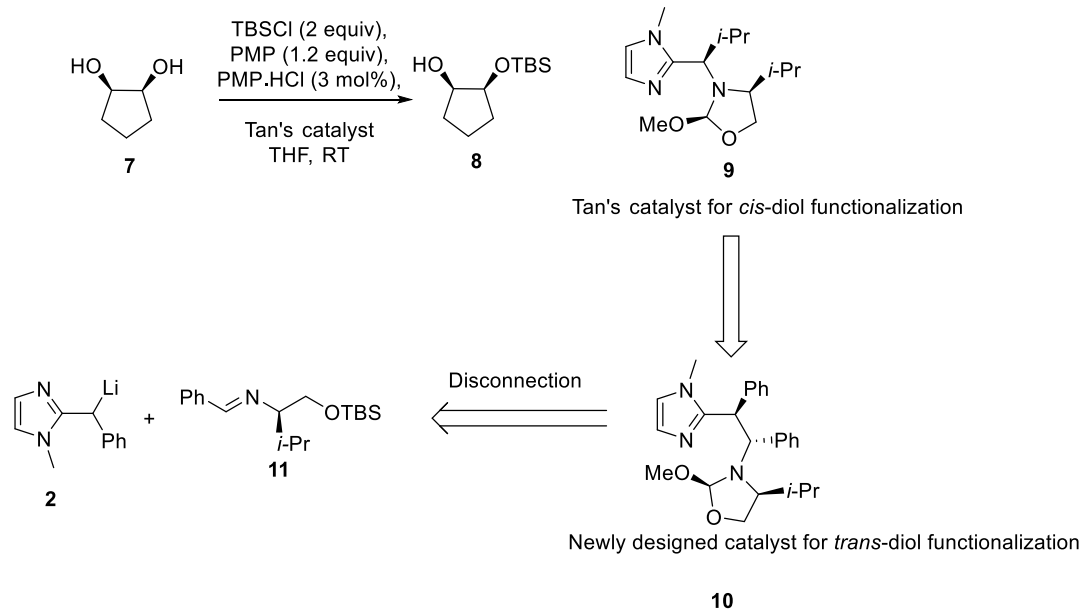


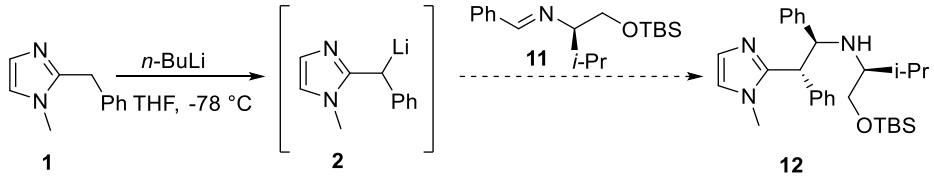
Figure 1. ORTEP of **5** and **6**.

With this newfound understandings of the fundamental reactivity and diastereoselectivity of this carbanion **2**, we became intrigued about the possibility of apply this technology to expand the Tan catalyst systems[9–11]. These new scaffolds would contain an additional stereogenic center and carbon spacer between the imidazole and the orthoaminoformate (e.g. compound **10**) (Scheme 3). This additional stereochemistry and spacer found in compound **10** showed preliminary computational evidence of expanded catalytic activity in the Tan desymmetrization / deracemization of polyols.



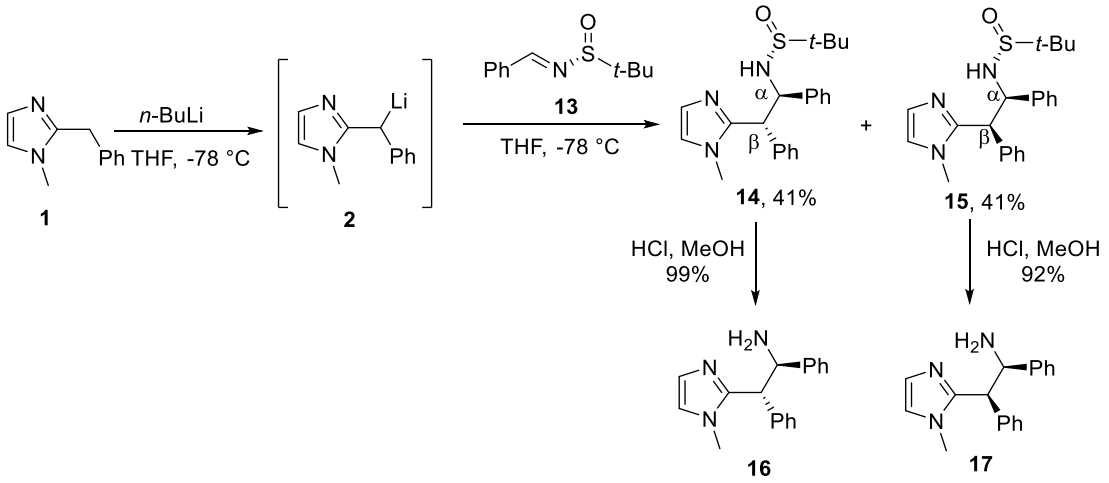
Scheme 3. Tan's catalyst and our modified version.

Initial attempt to synthesize catalyst **10** were made through addition of lithiated compound **2** to imine **11** (Scheme 4). Previously, imine **11** has been used for diastereoselective additions.[19–22] A variety of different conditions were screened – including the use of Lewis acids such as $TiCl_4$ and $BF_3 \bullet Et_2O$. Unfortunately, we did not observe successful coupling under any of these conditions – instead the imine **11** was recovered intact. One possible explanation for this problematic reactivity is the steric hinderance caused by the branching on the nitrogen atom of imine **11**. We speculated that placement of an electron withdrawing moiety on the imine might increase its overall reactivity and circumvent this reactivity issue.



Scheme 4. Unsuccessful route.

The successful application of the Elmann sulfinimine.[23–25] (*tert*-(*S*)-butylsulfinimine **13**) to the diastereoselective addition of the lithiated imidazole **2** is shown in Scheme 5. Two two chromatographically separable diastereomers **14** and **15** (1:1 dr) were observed in this transformation – with a single stereochemistry at the benzylic amine position attached to the chiral sulfinamine (denoted with an α notation on the structure) and an equal mixture at the benzylic imidazole position (denoted with a β notation on the structure) . These diastereomers **14** and **15** were assigned based on single crystal X-ray crystallographic analysis (Figure 3). Hydrolysis of **14** and **15** in methanolic hydrochloride solution gave the corresponding amine compounds **16** and **17** (Scheme 5). The coupling constants for the two adjacent benzylic protons in the *trans*-diphenyl amine **16** ($J = 9.5$ Hz) and *cis*-diphenyl amine **17** ($J = 7.5$ Hz) is consistent with the X-ray results for **14** and **15**.



Scheme 5. Synthesis of *trans* and *cis*-diphenyl amines **16**, **17**.

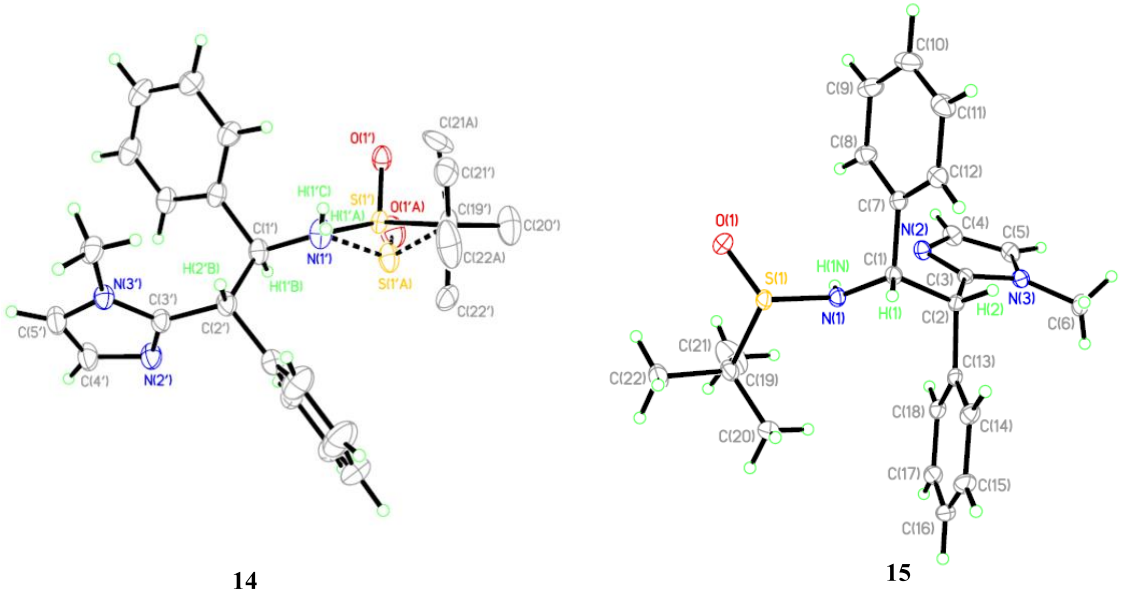
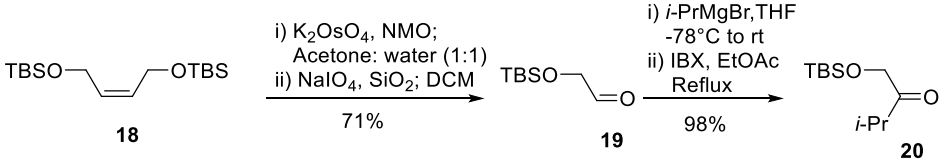


Figure 2. ORTEP of **14** and **15**.

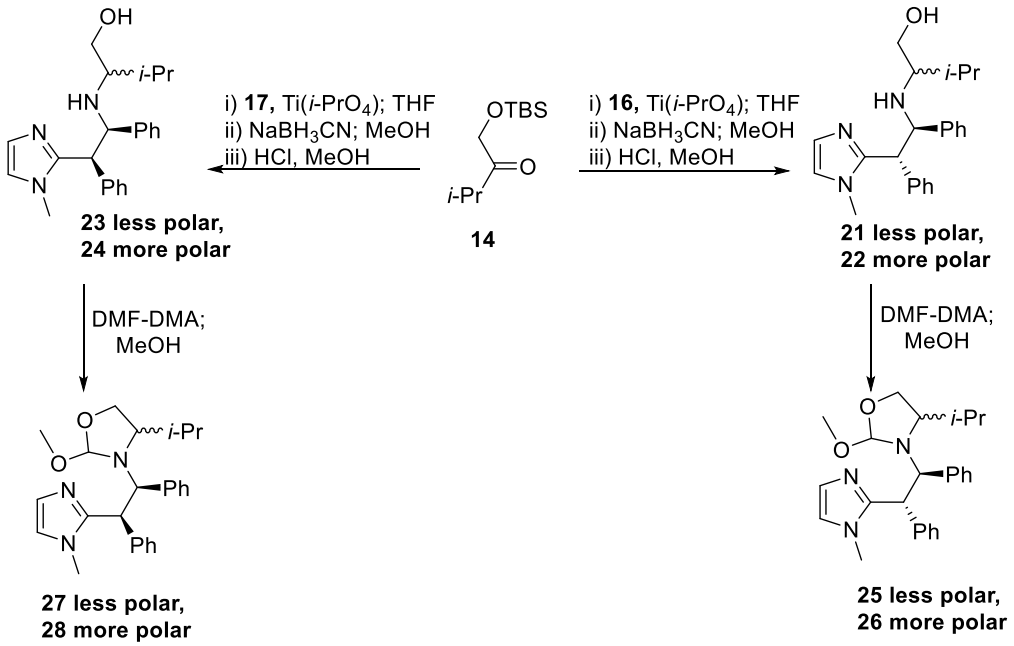
With the new amino imidazoles **16** and **17** now accessible, we shifted our focus to the remainder of the scaffold needed for the potential catalyst **10** (Scheme 6). Synthesis of the required precursor began with the known alkene **18**[26] by dihydroxylation to provide aldehyde **19**. Grignard addition of *iso*-propylmagnesium bromide to aldehyde **19** followed by oxidation of the secondary alcohol cleanly provided the desired ketone **20**.



Scheme 6. Synthesis of TBS protected ketone **20**.

Combination of the amino imidazoles **16** / **17** with ketone **20** is shown in Scheme 7.

Reductive amination of ketone **20** with amine **16** followed by silyl deprotection resulted in two separable alcohols **21** and **22** in an equal (1:1 dr) mixture. In a similar fashion, reductive amination of ketone **20** with epimeric amine **17** followed by silyl deprotection gave the corresponding alcohols **23** and **24** (1:1 dr). The identity of the newly form stereocenter in compounds **21-24** from this addition was not determined. Introduction of the *aza*-orthoformate moiety by reaction of these alcohols **21-24** with DMF-DMA gave the corresponding catalysts **25-28**. As was found in Tan's work, these compounds proved unstable when exposed to small amounts of moisture (even air) which hydrolyzed the *aza*-orthoformate moiety. Consequently, the catalysts were used crude in the kinetic resolution of *trans*-diols.



Scheme 5. Synthesis of oxazolidine catalysts **25-28**.

These generated catalysts were evaluated in the selective *trans*-diol functionalization[11] as shown in Table 1. We first explored a selective silylation using TBSCl. We confirmed that no appreciable yield was observed in the absence of catalysts **25-28** at 4°C (Entries 1-2). A similar behavior was observed for the 5-membered diol **7** at room temperature (Entry 3); however, the corresponding six-membered diol **29** did provide 72% yield of the mono-protected product **30** (Entry 4). Acylation proved too reactive on either diol, as the blank reaction proceeded easily at 4°C (Entries 5-6). With this knowledge, we focused our catalyst screening on the silylation at 4°C with the 5-membered diol **7**. Interestingly, catalyst **(26)** showed a diferential reactivity for *trans*-cyclopentanediol **7** over the 6-memberd *trans*-diol **29** with 47% yield (Entry 8). No enantioselectivity was observed in this transformation based on derivatization with Mosher's acid. Similar analysis of the product from the 6-membered diol **30** shown no enantioselectivity (Entries 11 and 12).

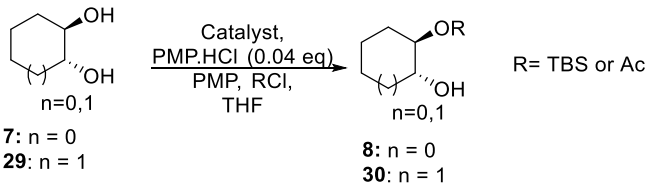


Table 1. Preliminary Exploration of Catalytic Activity of Compounds **25-28**.

Entry #	n	R	Cat. Load %	Temp (°C)	Yield	ee %
1	0	TBS	0	4	6	
2	1	TBS	0	4	25	
3	0	TBS	0	rt	6	
4	1	TBS	0	rt	72	
5	0	Ac	0	4	91	
6	1	Ac	0	4	86	
7	0	TBS	10 mol % **25**	rt	4	ND
8	0	TBS	10 mol % **26**	rt	47	0
9	0	TBS	10 mol % **27**	rt	3	ND
10	0	TBS	10 mol % **28**	rt	5	ND
11	1	TBS	10 mol % **25**	4	18	0
12	1	TBS	10 mol % **26**	4	22	0
13	1	TBS	10 mol % **27**	4	21	ND
14	1	TBS	10 mol % **28**	4	24	ND

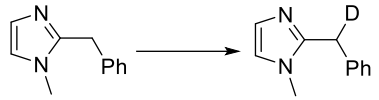
Conclusion

In summary, preliminary exploration into the fundamental reactivity of lithiated benzyl imidazoles has been disclosed. Selective lithiation takes place using *n*-BuLi at -78°C in dry THF. The electrophilic addition to benzaldehyde proceeds in low diastereoselectivity (circa 2:1 dr) favoring the *anti*-addition product. Addition to an imine required additional activation by a sulfinimine function. Derivatization of the imidazole-containing amines into Tan-like catalysts was accomplished. Modest catalytic activity was realized for selective protection for the *trans*-cyclopentanediol; however, no enantioselectivity was observed.

Experimental Details

General: Infrared spectra were recorded neat unless otherwise indicated and are reported in cm^{-1}. ^{1}H NMR spectra were recorded in deuterated solvents and are

reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230-400 mesh silica gel. Air and/or moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120°C or by flame, then cooled under argon. Dry THF and DCM were obtained via a solvent purification system. All other solvents and commercially available reagents were either purified via literature procedures or used without further purification.



1 **3**

Deuterated benzylimidazole 3: To a stirred solution of benzylimidazole **1** (25 mg, 0.145 mmol) in THF (0.95 mL) at -78°C was added sequentially *n*-BuLi (0.07 mL, 0.174 mmol, 2.5 M in hexanes). After 1h was added and CD_3OD (0.006 mL, 5.8 mg, 0.291 mmol). After 2 h, the cold bath was removed and the reaction mixture was stirred at room temperature. The reaction mixture was concentrated *in vacuo* and the % deuterium incorporation was determined using crude ^1H NMR to be 87%.

Supporting Information: Full experimental detail, ^1H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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Prof. Claudia Maier (OSU) and Jeff Morré (OSU) are acknowledged for mass spectra data. Drs. Ryne Johnston and Maduka Ogba are acknowledged for the early work on the computational analysis of the Tan chemistry.

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