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The synthesis of ethanolamine libraries from olefin scaffolds†

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Abstract

A solution-phase, multi-reaction sequence has been developed for the parallel synthesis of ethanolamine libraries. This approach uses 2,3-dibromopropene as a template for the synthesis of a small olefin sub-library, which is then further functionalized to form the final ethanolamine library. The methodology is demonstrated by the synthesis of a 5×4 array of ethanolamines.

We have been interested in the synthesis of olefinic libraries[1] from olefin templates.[2] These libraries contain several desirable properties for biological probes: they are readily synthesized in well defined relative geometries, the substituents can be varied systematically in space, and molecules of this type have proven valuable as pharmaceutical agents.[3] Another intriguing feature of olefin libraries is that the olefin component itself is a versatile functional group for further transformations in a 'libraries from libraries' type approach (Fig. 1).[4] In this paper, we report the synthesis of a small library of olefins and their transformation into a larger library of ethanolamines.

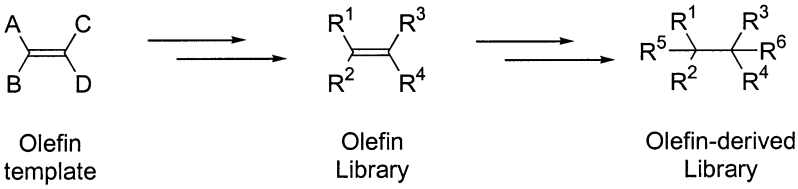

Figure 1. Olefin and olefin-derived libraries from simple multi-functional olefin templates

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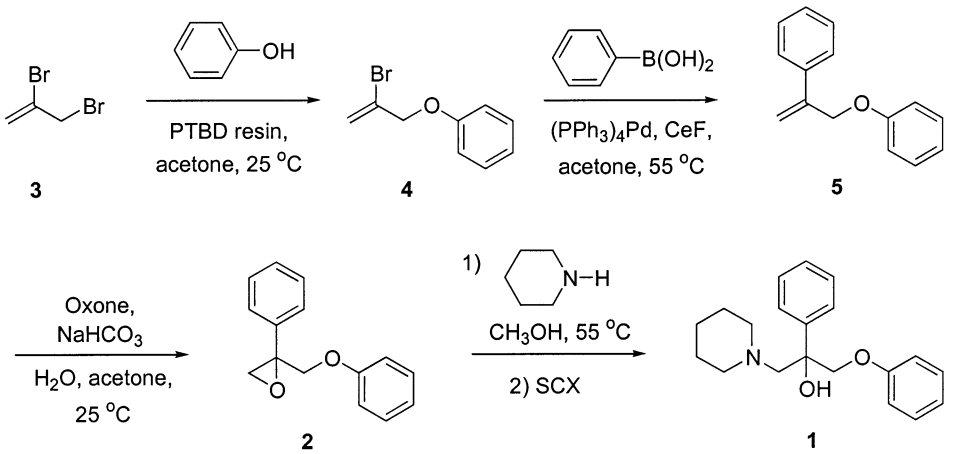
Although olefins are known to undergo a wide variety of transformations, we chose to first examine the construction of ethanolamines due to the ubiquitous presence of this functionality in a variety of biologically relevant small molecules.[5] The ethanolamines were envisioned to be obtained synthetically via a simple two step epoxide formation/aminolysis sequence,[6] with the required olefin starting materials for the epoxides assembled from 2,3-dibromopropene[2] by means of a phenolate substitution and subsequent Suzuki cross-coupling reaction. This synthetic strategy allows for the installation of diversity via the phenol, aryl boronic acid and amine moieties.

To test the viability of this synthetic approach in a parallel format, we examined the reaction sequence under conditions amenable to parallel synthesis (Scheme 1). In this case, the reactions were performed as discrete transformations. Compound **2** did not require chromatography, and when allowed to react with piperidine (0.9 equiv.) in methanol generated ethanolamine **1** in 90% yield.



Scheme 1.

Ideally, any reaction work-up, product isolation and purification should be reduced or eliminated for high throughput synthesis. Thus, the reaction of **3** (2 equiv.) with phenol (1 equiv.) in the presence of 2.2 equiv. of polystyrene-1,5,7-triazabicyclo[4.4.0]dec-5-ene (PTBD resin) as base[1,7] provided **4**, which then reacted smoothly with phenyl boronic acid to produce **5**, with no need to isolate the vinyl bromide prior to cross-coupling (Scheme 1). The crude phenylpropenyl ether **5** was epoxidized readily with dimethyldioxirane, generated in situ from Oxone® and $NaHCO_3$. Epoxide **2** was isolated by partitioning the compound between CH_2Cl_2 and H_2O. The aqueous layer was removed by means of solid supported liquid–liquid extraction[8] and evaporation of the solvent yielded crude epoxide **2**. Heating the crude epoxide with piperidine in MeOH produced the desired ethanolamine **1**, which was readily isolated by SCX chromatography.[9] The product was isolated in 45% overall yield and was >95% pure by ^1H NMR spectroscopic analysis. This sequence compressed three of the four synthetic transformations into a single multi-reaction sequence, thus eliminating the need for intermediate isolation.

We next explored the scope of the reaction sequence with respect to both the phenol and aryl boronic acid moieties to determine generally what functionality could be tolerated in a high throughput format. Some observed trends in this study are worthy of note. Phenols and boronic

acids used in this scope study that were unsuccessful are summarized in Fig. 2. We found that any oxidizable functionality present in either the phenol or the boronic acid components did not survive the epoxidation conditions. Furthermore, if an electron deficient phenol was used, the resulting phenolic ether (**4**) would undergo Pd-catalyzed ionization of the phenoxide competitively with oxidative insertion by Pd into the vinyl bromide under our Suzuki conditions (Scheme 2). We have made the observation previously that phenolate ions will attack the central carbon of the Pd π-allyl complex **6**, ultimately yielding the diphenoxy products **7**.[10] Additionally, heteroaryl boronic acids performed poorly in the Suzuki couplings.

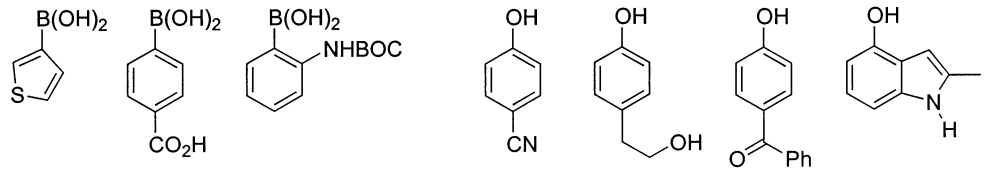
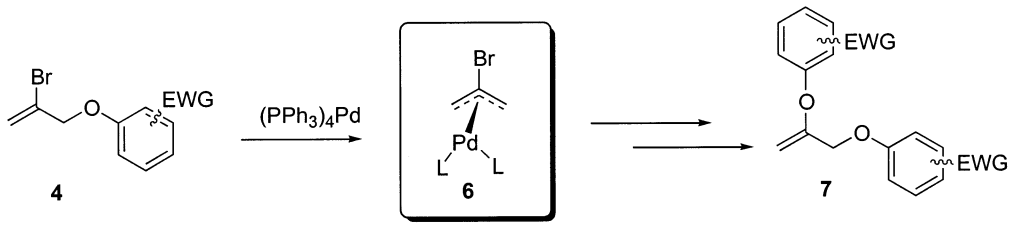
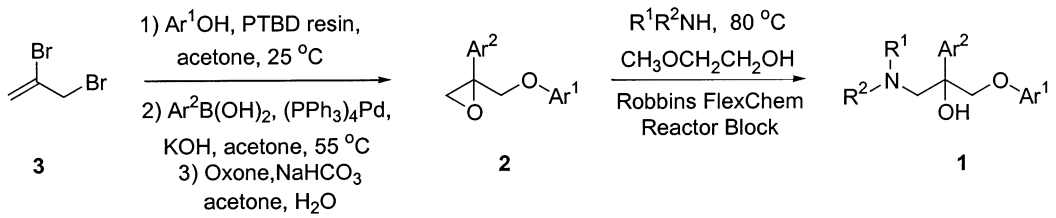


Figure 2. Unsuccessful phenol and boronic acid examples



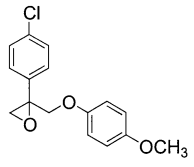
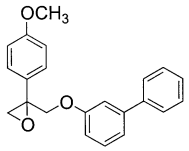
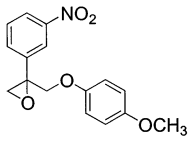
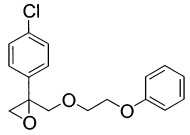
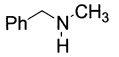
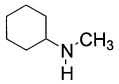
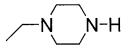
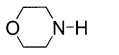
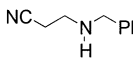
Scheme 2.

The final test of our approach was to synthesize the desired ethanolamines in an array format. To that end, the three-step tandem reaction sequence was employed to synthesize four epoxy ethers (vide supra). The ^{1}H NMR spectra of compounds **2** revealed that these intermediates were very clean with no visible signals arising from starting materials or potential byproducts. These compounds were then incubated with five amines in methoxyethanol in a Robbins 96-well FlexChem® Reactor Block (Scheme 3). Following purification by SCX and analysis by mass spectrometry, it was found that all wells contained the expected pseudo-molecular ion $(M+H)^+$ for the ethanolamine products (Table 1).



Scheme 3.

Table 1
Four by five array of epoxides and secondary amines[a] and their percent purity[b,c]

				
	94%; $(M+H)^+$, 412	97%; $(M+H)^+$, 454	89%; $(M+H)^+$, 423	89%; $(M+H)^+$, 426
	93%; $(M+H)^+$, 404	98%; $(M+H)^+$, 446	89%; M+1, 415	92%; $(M+H)^+$, 418
	94%; $(M+H)^+$, 405	92%; $(M+H)^+$, 447	81%; $(M+H)^+$, 416	83%; $(M+H)^+$, 419
	94%; $(M+H)^+$, 378	95%; $(M+H)^+$, 420	89%; $(M+H)^+$, 389	90%; $(M+H)^+$, 392
	56%; $(M+H)^+$, 451	76%; $(M+H)^+$, 493	72%; $(M+H)^+$, 462	64%; $(M+H)^+$, 466

[a] Reactions were carried out in a Robbins FlexChem® Reactor Block (epoxide/amine, 1:0.9) in methoxyethanol solvent at 80°C (see Experimental for full details).

[b] Purity is based on LC/MS data ($\lambda = 254$ and 280 nm) and analysis of the ^{1}H NMR spectra of the products following SCX chromatography. Mass spectra (250–700 amu) were obtained using a PE Sciex API 2000 triple quadrupole mass spectrometer using turboionspray as the method of ionization.

[c] The first term in each table entry is the percent purity. The second term is the observed pseudo molecular ion from the LC/MS spectra.

In summary, we have demonstrated a solution-phase, multi-reaction sequence for the generation of ethanolamine libraries from olefin templates. The use of this methodology for the creation of larger libraries of ethanolamines for general screening will be reported in due course.

Experimental: The following general procedure is representative for the aminolysis reactions performed in the Robbins FlexChem® Reactor Block. The four epoxide products from the tandem sequence (Scheme 3, products **2**) were weighed and each dissolved in 1.0 mL of methoxyethanol. Two hundred μL of each stock solution were loaded into four wells of the block (20 total). Five stock solutions of amines were prepared by dissolving 0.5 mmol of the amine in 1.0 mL of methoxyethanol, and 0.9 equiv. of each amine were dispensed orthogonally to the epoxides **2** to complete the array. After sealing the block, the mixtures were heated at 80°C for 16 h. Upon cooling to rt, the residues were concentrated and taken up in 10% AcOH/MeOH. The resulting solutions were passed through a 96-well filter plate containing 500 mg of SCX resin per well and the products were eluted with 20% NH_3/MeOH. In general, no signals corresponding to reactants or byproducts were observed in the ^{1}H NMR spectra. The yield/recovery range for the 20 compounds was from 30 to 60%.

Acknowledgements

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