A High-Throughput Screening Protocol for Fast Evaluation of Enantioselective Catalysts

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Abstract: A new high-throughput screening protocol that allows fast evaluation of enantioselective catalysts has been developed. The usefulness of norephedrine-derived β-amino alcohols as catalysts for the enantioselective alkylation of prochiral aldehydes has been determined by simultaneous screening of three representative substrates. GC analysis of the crude product mixture using a selectively modified cyclodextrin as the chiral stationary phase avoids time-consuming workup procedures. The chemical yield, enantioselectivity, substrate specificity, and catalytic activity of the chiral catalysts as well as the induced absolute configuration have been determined in a single screening experiment and two short GC runs.

Combinatorial chemistry provides a powerful tool for the development of new enantioselective catalysts.[1] Fast identification of efficient catalysts and optimization of reaction conditions require a high-throughput screening (HTS) methodology that is capable of answering a variety of questions.[2] Recently, Welch et al. reported a fast HTS protocol that utilizes HPLC-MS to evaluate yeast-mediated enantioselective reductions of diaryl ketones.[3] Kagan et al. applied multisubstrate screening to evaluate the asymmetric reduction of ketones using an oxazaborolidine derived from (*S*)-diphenylproline.[4] Herein, we report a multisubstrate screening methodology using enantioselective GC-MS analysis. Our approach allows fast determination of asymmetric induction, enantioselectivity, chemical yield, catalyst activity, and substrate specificity of a chiral catalyst by a single experiment. The HTS protocol was developed using (1*R*,2*S*)-*N*,*N*′-dibutylnorephedrine, **1**, and (1*R*,2*S*)-*N*-monobutylnorephedrine, **2**, as catalysts for the enantioselective alkylation of three representative aldehydes, Figure 1.[5] The development and evaluation of β-amino alcohols that promote the enantioselective alkylation of prochiral aldehydes using organozinc reagents remains an active area of investigation.[6] Chiral ligands used to date usually afford high stereoselectivity only for certain types of aldehydes. A fast and comprehensive screening protocol that is capable of determining a catalyst's applicability to linear, branched, and aromatic aldehydes is most desirable for the development of new catalysts.

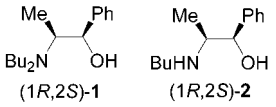
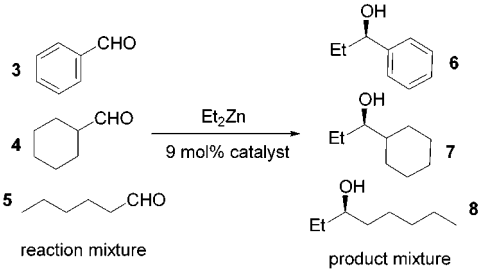


Figure 1. Structure of catalysts **1** and **2**.

Scheme 1. Multisubstrate HTS Using Aldehydes 3−5



Chiral catalysts **1** and **2** were synthesized from commercially available (1*R*,2*S*)-norephedrine.[7] Benzaldehyde, **3**, cyclohexanecarboxaldehyde, **4**, and hexanal, **5**, were chosen as substrates to represent different types of aldehydes, i.e., linear and branched aliphatic as well as aromatic aldehydes, Scheme 1. Racemic 1-phenylpropanol, **6**, 1-cyclohexylpropanol, **7**, and 3-octanol, **8**, were prepared via Grignard reaction from corresponding aldehydes **3**−**5**, respectively, and used for GC method development as well as references for mass spectrometry.[8] Comparison of MS data of each reference with MS spectra obtained for the nonracemic alcohol mixtures of our screening experiments allowed us to exclude coelution of impurities during GC analysis. Thus, we were able to (a) unequivocally identify products and (b) accurately determine the enantiomeric excess of each alcohol from the crude product mixture. Notably, our screening procedure avoids time-consuming purification steps.

GC analysis of the reaction mixture containing prochiral aldehydes **3**−**5** and of the crude product mixture obtained by enantioselective alkylation with diethyl zinc allowed fast evaluation of norephedrine-derived catalysts **1** and

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(8) Racemic alcohols **6**−**8** were prepared from aldehydes **3**−**5** using ethylmagnesium chloride. Each alcohol was purified by flash chromatography and identified by NMR spectroscopy.

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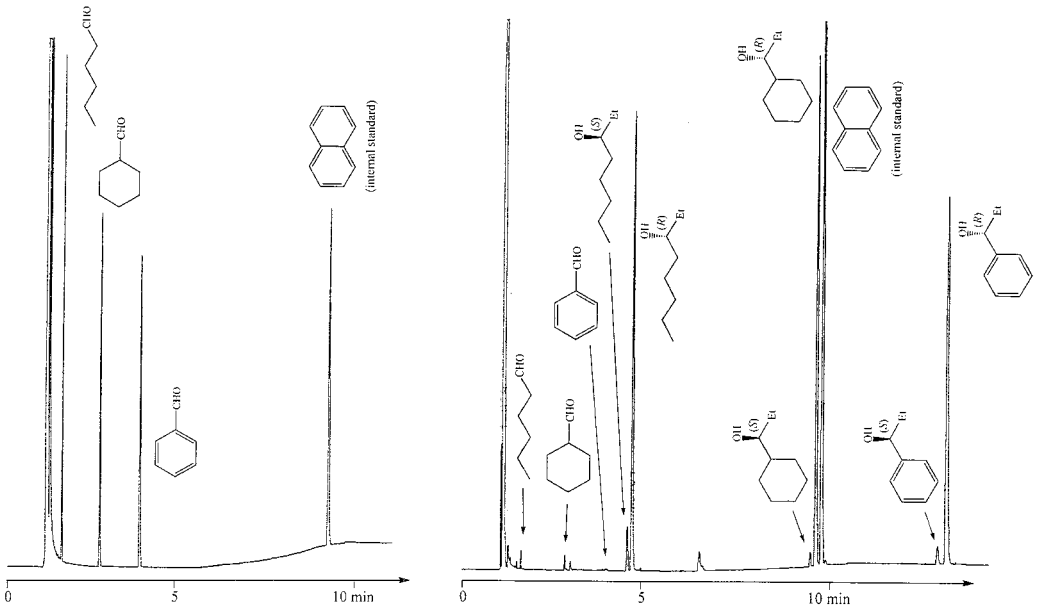

Figure 2. Gas chromatogram of the reaction mixure (left) and GC separation of a representative product mixture obtained by multisubstrate HTS using (1*R*,2*S*)-**1** as the catalyst (right).

2. Optimization of chromatographic conditions using octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin[9] as the chiral stationary phase enabled us to separate aldehydes **3**−**5**, naphthalene, and the enantiomers of alcohols **6**−**8** in a single run, Figure 2. GC analysis of the reaction mixture containing the three aldehydes and naphthalene as the internal standard provided individual response factors for calculation of chemical yields.[10] In addition, the enantiomeric excess and absolute configuration of chiral alcohols **6**−**8** were easily obtained from the same run. No indication of coelution of impurities with enantiomers of **6**−**8** was observed by GC-MS. Since aldehydes **3**−**5** were converted simultaneously, i.e., under identical reaction conditions, comparison of the substrate specificity and application spectrum of the catalyst was greatly facilitated, vide infra. Thus, our HTS protocol provides a comprehensive and time-efficient catalyst evaluation that requires only one experiment and two short GC-MS or GC-FID runs of less than 15 min.

Simultaneous screening of the enantioselective alkylation of aldehydes **3**−**5** revealed high enantioselectivity and catalytic activity of (1*R*,2*S*)-**1** for aldehydes **3** and **4**, Table 1. Alcohols (*R*)-**6** and (*R*)-**7** were obtained in almost quantitative yields and ees above 90% at 0 °C. Conversion of **5** to (*R*)-**8** proceeded with only 84% ee and 88% chemical yield due to incomplete aldehyde conversion at 0 °C after 16 h. Interestingly, the yield of **8** significantly improved to 97% at room temperature without compromising the enantioselectivity. The multisubstrate screening results clearly show that (1*R*,2*S*)-**1** exhibits a higher enantioselectivity for aromatic and branched aliphatic substrates than for linear aliphatic aldehydes. Most importantly, our HTS protocol affords reproducible results that are in excellent agreement with data obtained from individual screening experiments, Table 2. Enantioselectivites and chemical yields obtained by both screening procedures do not vary more than 3%.

Table 1. Multisubstrate Screening Results

run	catalyst	temp (°C)	aldehyde	% ee (±3%)[a]	configuration[a]	% yield (±3%)[b]
	1	0	**3**	91	(*R*)	97
1	**1**	0	**4**	97	(*R*)	96
	1	0	**5**	84	(*R*)	88
	1	25	**3**	92	(*R*)	99
2	**1**	25	**4**	95	(*R*)	97
	1	25	**5**	83	(*R*)	97
	2	25	**3**	71	(*R*)	>99[c]
3	**2**	25	**4**	46	(*R*)	93
	2	25	**5**	43	(*R*)	98

[a] Enantiomeric excess of alcohols **6**−**8** was determined by enantioselective GC. Elution order of enantiomers of alcohols **6**−**8** using octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin as the chiral stationary phase was determined according to the known chiral induction of **1**.[5c] [b] Percent yields are calculated on the basis of GC analysis using naphthalene as the internal standard.[10] [c] No starting material was detected.

Table 2. Individual Screening Results

run	catalyst	temp (°C)	aldehyde	% ee (±3%)[a]	configuration[a]	% yield (±3%)[b]
1	**1**	0	**3**	92	(*R*)	>99[c]
2	**1**	0	**4**	94	(*R*)	>99[c]
3	**1**	0	**5**	84	(*R*)	88
4	**2**	25	**3**	69	(*R*)	98
5	**2**	25	**4**	47	(*R*)	89
6	**2**	25	**5**	35	(*R*)	84

[a] Enantiomeric excess of alcohols **6**−**8** was determined by enantioselective GC. Elution order of enantiomers of alcohols **6**−**8** using octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin as the chiral stationary phase was determined according to the known chiral induction of **1**.[5c] [b] Percent yields are calculated on the basis of GC analysis using naphthalene as the internal standard.[10] [c] No starting material was detected.

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(10) Individual response factors [area(aldehyde) × mg(standard)/area(standard) × mg(aldehyde)] were determined for all three aldehydes by GC analysis of the reaction mixture. Determination of the ratio of the area of each aldehyde to the area of naphthalene obtained from a second GC run of the product mixture allowed calculation of the remaining starting material. Dilution experiments revealed excellent linearity of aldehyde responses over the concentration range obtained in reaction and product mixtures. Total area % of side products proved to be less than 2% in all cases. Thus, we were able to calculate aldehyde conversion as well as the chemical yield. Calculation of the yield using a standard solution of alcohols **6**−**8** and naphthalene as the internal standard afforded similar results. However, reproducibility and precision were unsatisfactory since response factors of alcohols **6**−**8** varied significantly from run to run.

Comparison of our screening results reveals superior catalytic performance of β-amino alcohol **1** over **2**, Table 1. Both catalysts promote formation of alcohols exhibiting the (*R*)-configuration. Enantioselective alkylation of aldehydes **3**−**5** using catalyst (1*R*,2*S*)-**2** proceeds with high yields but only moderate ees at room temperature. Results obtained for conversion of aldehydes **3** and **4** to their corresponding alcohols by multisubstrate and individual screening are in very good agreement. However, simultaneous screening somehow affords a higher enantioselectivity and yield for the formation of (*R*)-**8** from **5**, Table 2.

One might expect that the usefulness of multisubstrate HTS as described herein would be limited to catalytic reactions that do not exhibit autocatalysis or catalyst poisoning by reaction products. However, it is well-known that the enantioselective alkylation of aldehydes promoted by β-amino alcohols is often accompanied by autocatalysis and nonlinear effects.[11] Nonchiral additives have also been reported to affect the catalytic performance of β-amino alcohols.[12] The increase of yield and enantioselectivity observed for conversion of hexanal in the presence of benzaldehyde and cyclohexanecarboxaldehyde might result from some catalytic activity of (*R*)-alkoxides formed during catalysis.[13] Nevertheless, results obtained using our HTS protocol are in very good agreement with individual screening of each aldehyde. Simultaneous substrate screening as described herein is also likely to be very useful for optimization of reaction conditions and for evaluation of catalyst candidates for a variety of other enantioselective reactions.

In summary, we have demonstrated that fast evaluation of β-amino alcohols as catalysts for the enantioselective alkylation of prochiral aldehydes using diethylzinc can be accomplished by multisubstrate high-throughput screening. The applicability of norephedrine-derived catalysts toward linear, branched, and aromatic aldehydes has been determined by simultaneous screening of representative substrates. GC analysis of the crude product mixture using a selectively modified cyclodextrin as the chiral stationary phase avoids time-consuming workup procedures. Thus, the chemical yield, enantioselectivity, substrate specificity, and catalytic activity of the chiral catalysts as well as the induced absolute configuration have been determined in a single screening experiment and two short GC runs using naphthalene as the internal standard.

Experimental Section

Chemicals were of reagent grade and purchased from Aldrich. All reactions were carried out under a nitrogen atmosphere and anhydrous conditions.

General Procedure for Screening Catalyst 1. A solution of catalyst **1** (0.04 mmol, 9 mol %) and the aldehyde mixture (0.47 mmol of all three aldehydes) in 2 mL of anhydrous hexanes was stirred at room temperature for 20 min and then cooled to 0 °C. After 40 min, Et_2Zn (1.1 mL, 1 M in hexanes) was added dropwise. The solution was stirred for 16 h at 0 °C and quenched with 5 mL of saturated NH_4Cl. The aqueous layer was extracted three times with CH_2Cl_2. The organic layers were combined and used for GC analysis without further workup.

General Procedure for Screening Catalyst 2. A solution containing **2** and diethylzinc was stirred at room temperature for 40 min. After the solution was cooled to 0 °C, the aldehyde mixture was added dropwise. The solution was allowed to come to room temperature and stirred for 16 h. The workup procedure described above was followed by GC analysis of the crude product mixture.

GC Analysis. Aldehydes **3**−**5**, naphthalene, and enantiomers of alcohols **6**−**8** were separated by GC using octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin (60% in OV 1701, 30 m) as the chiral stationary phase. Temperature program: 90 °C for 5 min, then 7 °C/min to 115 °C. Enantioselectivity α: 1.02 (**6**), 1.02 (**7**), 1.04 (**8**).

Supporting Information Available: Experimental procedure for the synthesis of catalysts **1** and **2** and spectroscopic data for **1** and **2** This material is available free of charge via the Internet at http://pubs.acs.org.

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