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Machine-Assisted Preparation of a Chiral Diamine Ligand Library and In Silico Screening Using Ab Initio Structural Parameters for Heterogeneous Chiral Catalysts

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Abstract: A ligand library containing 31 chiral diamines was synthesized using a flow-based semi-automatic reductive amination system. These ligands were evaluated in a continuous-flow asymmetric 1,4-addition reaction with a heterogeneous Ni catalyst. Based on the experimental results of ab initio DFT calculations, a prediction model for enantioselectivities was successfully constructed. Furthermore, virtual screening of possible ligands was conducted to identify promising structures, which showed good enantioselectivities in experiments.

Keywords: flow chemistry; heterogeneous catalysis; automatic synthesis; machine learning; virtual screening

Toward a sustainable society, a paradigm shift from homogeneous catalysts to heterogeneous catalysts in organic synthesis is desired since recovery and reuse of catalysts can reduce the environmental burden significantly. Furthermore, continuous-flow reactions using heterogeneous catalysts have advantages over current batch reactions in terms of environmental compatibility, efficiency, and safety, and are expected to play important roles in future fine-chemical production.[1] Therefore, rapid research and development of heterogeneous catalysts that can be used for flow reactions is in strong demand.[2]

The synthesis of catalysts and their associated ligands usually relies on time-consuming and laborious manual processes, which prevent chemists from constructing large datasets that can be analyzed.[3] There have been several efforts to make "robot chemists" in batch systems, which could set up reactions the same as humans.[4,5] However, the overall system tends to be large, expensive, and limited in possible operations, which hamper the widespread use of such automated methods. By contrast, one of the merits of conducting chemical reactions in continuous-flow systems is their suitability for automation. If a continuous-flow system is simply combined with an autosampler and a fraction collector at the inlet and the outlet, respectively, the system could be used to conduct multiple reactions sequentially.[6,7]

The experimental evaluation of the performance of designed metal/ligand catalyst combinations is another important part of research and development. Recently, data-intensive approaches have attracted much attention from all scientific fields, including synthetic organic chemistry.[8,9] To predict the performance of catalysts, many models have been developed based on various molecular parameters such as Hammett,[10] Taft,[11] Charton,[12] and Sterimol parameters.[13] To include synergistic nonlinear variations, Sigman et al. proposed that interlinked effects of parameters be embedded in molecular vibration modes, and they demonstrated the utility of this approach for many chemical systems.[14] We hypothesized that slight variations of the optimized molecular structure also reflected complex interactions between substituents and served as relevant parameters. These parameters can be included in the standard output of molecular structure optimization and can be input directly to fit the model.

Catalytic asymmetric C–C bond-forming reactions are essential for the production of fine chemicals; however, heterogeneous catalysts are less explored than homogeneous catalysts. We recently reported heterogeneous chiral Ni catalysts[15] for asymmetric 1,4-addition reactions of 1,3-dicarbonyl compounds with nitroalkenes.[16,17] The catalysts showed high activity and enantioselectivity and were applicable for

continuous-flow reactions. To further improve the catalytic performance, further screening of chiral ligands on the heterogeneous catalyst is necessary. However, this is time-consuming because catalysts with each ligand need to be prepared individually. We think that rapid screening could be performed more efficiently using a method in which chiral ligands are flowed to a column packed with a ligand-free heterogeneous Ni catalyst to construct an active species in the column.

Herein, we describe the construction of a semi-automatic system for the synthesis of a chiral diamine ligand library based on continuous-flow reductive amination[18] and evaluate the library in continuous-flow asymmetric 1,4-addition reactions with heterogeneous chiral Ni catalysts. Experimental yields and enantioselectivities were determined with 31 ligands, which could be synthesized from commercially available inexpensive aldehydes. Moreover, we have shown that a reliable prediction model could be constructed based on nonempirical DFT calculations without human interpretation. We have virtually screened all possible ca. 10^3 substitution patterns, most of which are commercially unavailable or highly expensive, in silico and identified promising ligands, which have been confirmed to give good enantioselectivities by additional experiments.

The chiral diamine ligand library was synthesized by direct reductive amination of (1*R*,2*R*)-(−)-1,2-cyclohexanediamine and various aromatic aldehydes in a continuous-flow method based on our previous report (Scheme 1).[18] A column (SUS, 4.6×250 mm diameter) packed with Pt/C was heated at 40 °C, and a solution of an aldehyde and a diamine in a mixture of toluene and ethanol (95:5) was pumped into the column at 0.2 mL/min. A stream of 20 mL/min of H_2, regulated by a mass-flow controller, was connected to the system through a T-shaped mixer at the inlet of the column. The reaction was conducted for 100 min, and then the column was subsequently washed by flowing solvent at 1 mL/min for 20 min. Due to the robustness and long lifetime of the Pt/C catalyst, all the ligands could be synthesized using the same column and repeating the reaction and wash cycle. Changing solutions of starting materials, washing the column, and collecting the solutions after the reactions were fully automated. Collected fractions were combined, concentrated, and purified by an automatic column chromatography system. Using this reaction system, we have synthesized using aminosilica (NH-SiO_2) chiral diamine ligands (Figure 1).

We then evaluated the chiral diamine ligand library in an asymmetric 1,4-addition reaction with a heterogeneous chiral Ni catalyst. A Ni-diamine complex prepared from nickel acetate and *N*,*N*′-dibenzylethylenediamine was used as a precursor (Scheme 2). *N*,*N*′-Dibenzylethylenediamine acted as a dummy ligand and was removed during the calcination step. This complex and mesoporous silica (MCM-41) were mixed in MeCN for 2 h and then filtered. Obtained solids were calcinated at 450 °C for 6 h to afford Ni@MCM-41. Ni loading of the catalyst was determined to be 0.295 mmol/g by ICP-OES analysis. This catalyst did

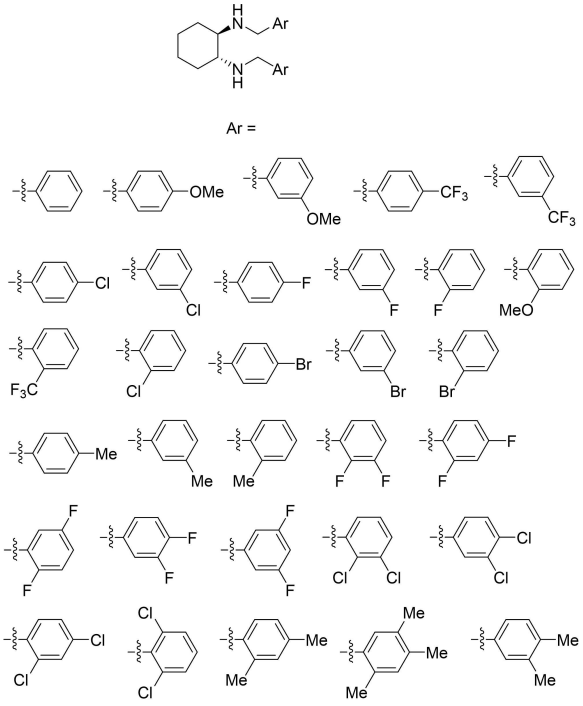
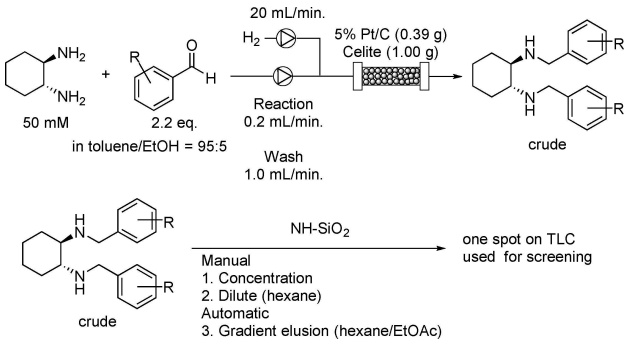
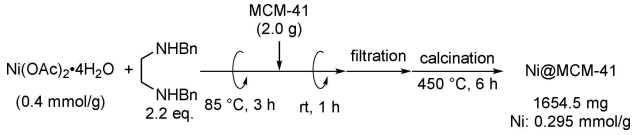


Figure 1. Experimentally Synthesized Chiral Diamine Ligand Library.



Scheme 1. Synthesis of a Chiral Diamine Ligand Library.

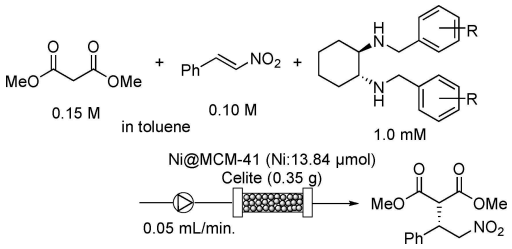


Scheme 2. Synthesis of Ni@MCM-41.

not have activity because the dummy ligand was burned out.

After optimizing the reaction conditions, a flow system to evaluate chiral ligands was set up as shown in Scheme 3. A toluene solution of starting material and chiral diamine ligand was pumped to a flow reactor (SUS column, 5×50 mm diameter). The column was packed with a mixture of Ni@MCM-41 (13.84 µmol) and Celite (0.35 g), and was heated at 45 °C. It was found that the results could be affected by the ligand of previous run even after extensive washing of the column. Therefore, we prepared the column packed with a mixture of fresh catalyst and Celite in each reaction to avoid the contamination of ligand. To generate active species inside the column, pretreatment of the column with a chiral diamine ligand solution was performed before starting the reaction. The ligand was supplied to the column to maintain catalytic activity. We performed the reaction for 19 h, and fractions were collected every hour. The fractions collected at 1–2, 2–3, 3–4, and 18–19 h were analyzed by ^{1}H NMR spectroscopy to determine yields, and all fractions were analyzed by HPLC to estimate yields and enantioselectivities (Figure 2).

With experimental data in hand, we studied regression analysis to establish the prediction model. We chose the LASSO regression model because it simplified the interpretation of the resulting model. In this study, minimal molecular descriptors were selected based on their applicability to virtual screening. HOMO and LUMO energies (25 energies each), Mulliken charges of atoms, bond lengths, and angles were collected by DFT calculations (B3LYP/6-31G(d)) of aromatic moieties of ligands as parameters of chiral ligands. We constructed a model to predict enantioselectivities, and coefficients of parameters are summarized in Table 1. Our model could predict the outcome with total seven parameters, two HOMO energy levels, two LUMO energy levels, one bond length, and two bond angles (Figure 3). The validity of the model was confirmed by leave-one-out cross validation to ensure the prediction power for the out of training dataset. No Mulliken charges were chosen. We also tried to construct a model for yield prediction. However, we failed to obtain a valid model, which might indicate that other parameters in addition to aromatic moieties of the ligands would be needed to be considered, or that some of the reactions did not reach steady states.



Scheme 3. Flow System to Evaluate Chiral Diamine Ligands.

After constructing the prediction model, we performed virtual screening of possible ligands. Five kinds of substituents (H, Me, CF_3, F, and Cl) at five positions could be assumed based on our training data. DFT calculation inputs for all $5^5 = 3125$ ligands were generated by the program and virtually evaluated (Figure 4). Among top-performing ligands, we selected three valid ligands, namely 3,5-dimethyl, 2,3-dimethyl, and 3-fluoro-5-methyl substituted ligands, based on commercial availability, for further experimental validation of the prediction model (Table 2). All three ligands showed good enantioselectivities among the

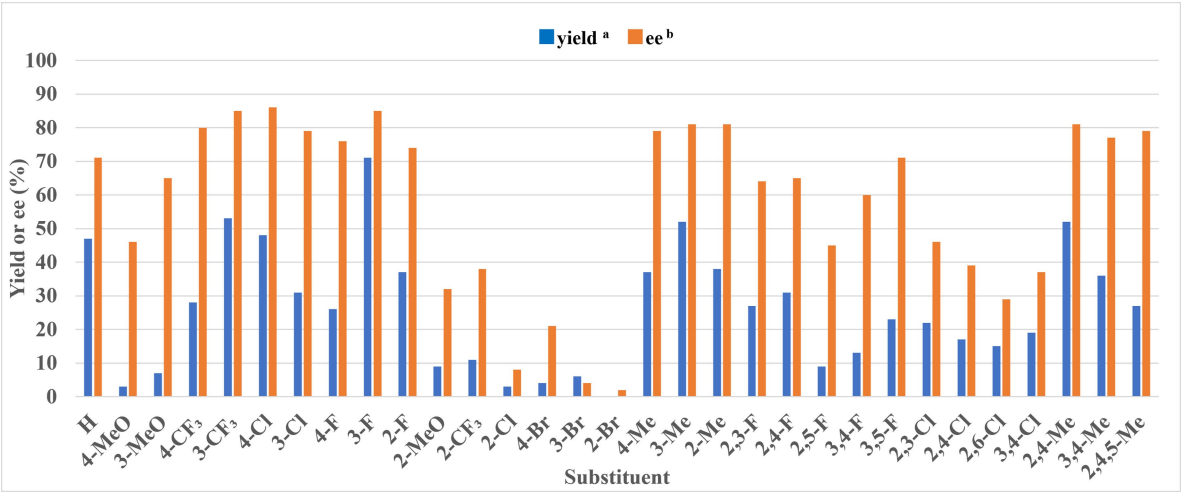


Figure 2. Yield and Enantiomeric Excess of the Fraction Collected at 18–19 h. For 3Br the fraction was collected at 12–13 h. a) Determined by ^{1}H NMR analysis. b) Determined by HPLC analysis.

Table 1. Coefficients of Parameters in the LASSO Model.

Parameter	Coefficient	Parameter	Coefficient
HOMO21	−0.03	R5	−7.83
HOMO22	−0.33	A3	−1.85
LUMO7	5.52	A5	3.98
LUMO14	−4.03		

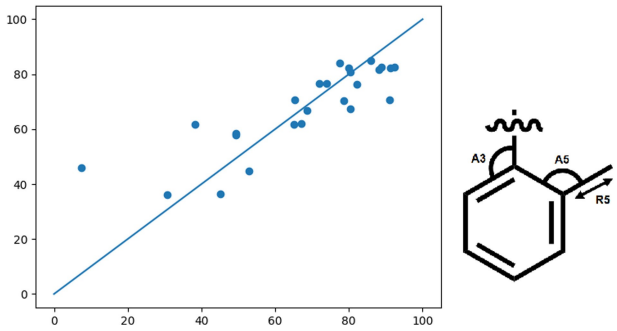


Figure 3. Correlation between Experimental and Predicted Enantioselectivities.

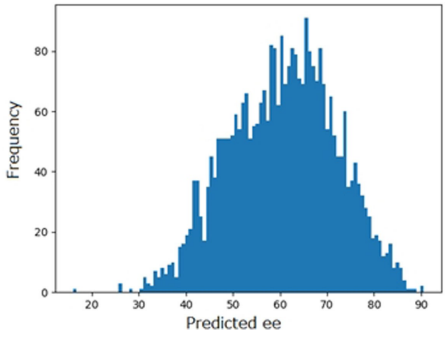


Figure 4. Histogram of the Predicted Enantioselectivities of Virtual Screening Set.

Table 2. Evaluation of New Ligands.

R	Experimental ee (%)	Predicted ee (%)
3,5-Me	73	86.01
2,3-Me	80	76.66
3-F-5-Me	75	78.71

dataset based on experimental results. Furthermore, it was also predicted that the highest enantioselectivity using these types of chiral ligands was ca. 90% ee, and that other types of ligands would be needed to be found to further improve the enantioselectivity.

In conclusion, we have set up a semiautomatic synthesis and evaluation system for continuous-flow reactions with heterogeneous chiral catalysts. The system is inexpensive and configurable. Moreover, we have developed a novel analysis procedure for chemical reactions that is based on ab initio theoretical calculation results and is suitable for computational generation of a vast set of parameters. With this protocol, we could readily prepare a large dataset of imaginary ligands for the heterogeneous chiral catalysts and virtually screened many possible ligands to successfully identify promising ligands worth evaluating experimentally. To our knowledge, this is the first study that allowed suitable heterogeneous chiral catalysts to be predicted based on machine-assisted library synthesis and in silico virtual screening. Our total system, readily available continuous-flow-based automatic synthesis, combined with analysis and in silico screening, paves the way for next-generation research in synthetic organic chemistry.

Experimental Section

Procedure for the Synthesis of Chiral Diamine Ligand Library

A 250×4.6 mm diameter SUS column was packed with a previously prepared mixture of Pt/C (5%, 0.39 g) and Celite (1.00 g). Blank solvent (toluene/ethanol = 95:5) was flowed at 1.0 mL/min at room temperature for several minutes until the system had been stabilized. A H_2 gas stream (20 mL/min) was connected through a T-shape mixer and the flow rate of blank solution was set at 0.2 mL/min. The column was heated at 40 °C. After stabilization of the system, inlet of the flow was put into the reaction mixture, solution of chiral diamine (50 mM) and aromatic aldehyde (2.2 eq.) in toluene/ethanol = 95:5. The reaction was conducted for 100 minutes and the collected eluent was concentrated and purified with automatic chromatography system (NH–SiO_2, hexane/EtOAc gradient). Immediately after the reaction, the inlet of the flow was put into the blank solvent to wash the column for reuse. The blank solvent was flowed at 1.0 mL/min for 20 minutes. After the washing, the inlet of the flow was put into the next reaction solution to conduct the following synthesis.

Procedure for the Synthesis of Ni@MCM-41

In a 50 mL two-necked round-bottom flask, $NiBr_2$ (0.8 mmol) and N,N′-dibenzylethylenediamine (0.176 mmol) were stirred in MeCN (40 mL) at 85 °C for 3 h. MCM-41 (2.0 g), which was used after drying at 100 °C for 1 h under reduced pressure, was added and stirred for 1 h. The reaction mixture were filtrated and obtained solid was washed with DCM and dried under reduced pressure. Solid material was calcinated at 450 °C for 6 h under air. The Ni loading of obtained catalyst was determined by ICP analysis.

Procedure for the Evaluation of Ligand Library in Asymmetric 1,4-Addition Reaction

A 5×50 mm diameter SUS column was packed with a previously prepared mixture of Ni@MCM-41 (Ni: 13.84 μmol) and Celite (0.35 g). Blank toluene was flowed at 1.0 mL/min. at 45 °C for several minutes. Ligand solution (in toluene, 2 mM,

15 mL) was flowed at 1.0 mL/min. at 45 °C for 2 h in a circulation manner. After pretreatment of column with ligand, inlet of the flow was put into the reaction mixture, solution of dimethyl malonate (1.5 eq.), β-nitrostyrene (0.1 M), chiral ligand (1 mol%), and 1,2,4,5-tetramethylbenzene (internal standard, 0.5 eq.) in toluene. The reaction was performed for 19 h and fractions were collected every hour. Fractions collected at 1–2, 2–3, 3–4, and 18–19 h after starting the reaction were analysed by ^{1}H NMR to determine yield. All fractions, after the treatment with silica gel, were analysed by HPLC to determine ee.

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