Machine-learning assisted efficient exploration of suitable flow reaction conditions for organocatalyzed domino reaction

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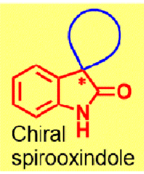
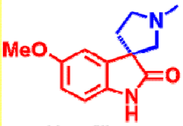
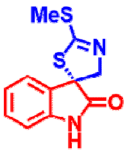
① *Chiral spirooxindoles*



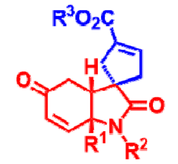
Chiral spirooxindole



Horsfiline

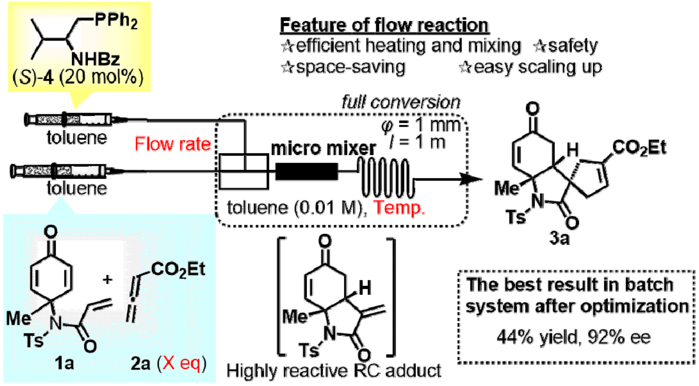


Spirobrassinin



Spirooxindole analogues
(This work)

② *Rauhut-Currier/ [3+2] annulation in flow system*



(*S*)-**4** (20 mol%)

3a

1a **2a** (X eq)

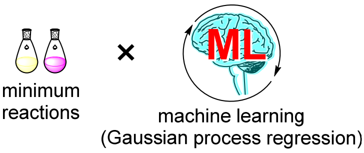
Highly reactive RC adduct

Feature of flow reaction
☆efficient heating and mixing ☆safety
☆space-saving ☆easy scaling up

The best result in batch system after optimization
44% yield, 92% ee

Three factors affecting to yield
① quantity of **2a** ② Temperature ③ Flow rate

③ *Machine learning (ML) assisted reaction exploration*



minimum reactions

machine learning
(Gaussian process regression)

High efficiency
☆ save cost ☆ save chemicals
☆ save time ☆ save manpower
☆ save energy ☆ reduce waste

Feature of Gaussian process regression (GPR)
non-parametric approach that can be used to make exploration and prediction based on a set of observed data

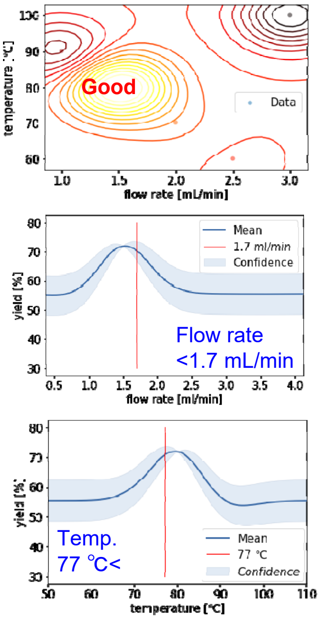
Our approach
・optimizing two parameters simultaneously
・predicting the next parameter value from the observed data through GPR

④ *Screening and exploring reaction conditions*

Table 1. ***Screening of temperature and flow rate***

Entry	Flow rate (mL/min)	Temp. (°C)	2a (eq)	NMR yield (%)
1	**1.0**	**90**	2.0	**49**
2	**1.5**	**80**	2.0	**72**
3	**2.0**	**70**	2.0	**58**
4	**2.5**	**60**	2.0	**55**
5	**3.0**	**100**	2.0	**43**

GPR results from Table 1



GPR results from Table 2

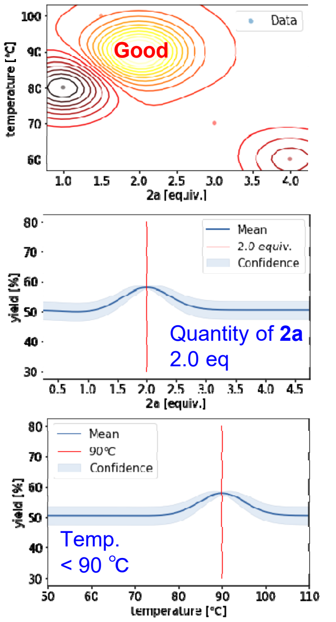
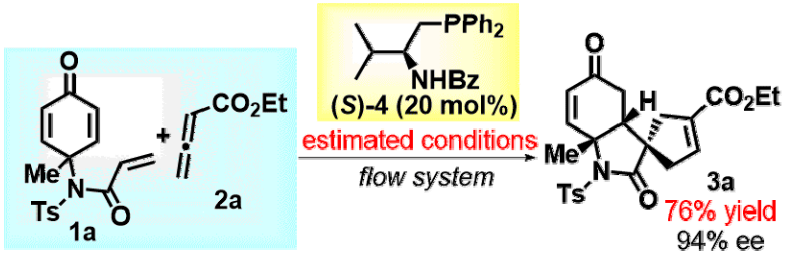


Table 2. ***Screening of temperature and quantity of 2a***

Entry	Flow rate (mL/min)	Temp. (°C)	2a (eq)	NMR yield (%)
1	1.7	**80**	**1.0**	**45**
2	1.7	**100**	**1.5**	**51**
3	1.7	**90**	**2.0**	**58**
4	1.7	**70**	**3.0**	**50**
5	1.7	**60**	**4.0**	**48**

⑤ *Application to a practical reaction*

Estimated reaction conditions from GPR and 10 experimental data
flow rate = 1.7 mL/min, temperature = 80 °C, quantity of **2a** = 2.0 eq



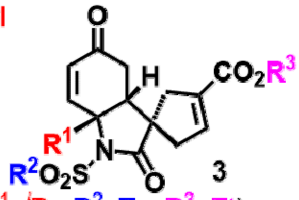
1a **2a**

(*S*)-**4** (20 mol%)

3a
76% yield
94% ee

⑥ *Substrate Scope*

R^1: aryl, alkyl, vinyl alkynyl
R^2: Ph, PMP, Me
R^3: Et, Bn
19 examples
up to 92% yield (R^1: ^{i}Pr; R^2: Ts; R^3: Et)
up to 98% ee (R^1: *p*-^{t}BuC$_6$H$_4$; R^2: Ts; R^3: Et)



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Chem. Commun. **2020**, *56*, 1259.

Our other sequential reactions, see: *ChemistrySelect* **2016**, *1*, 5414; *J. Am. Chem. Soc.* **2016**, *138*, 11481; *Chem. Pharm. Bull.* **2017**, *65*, 997; *Org. Lett.* **2017**, *19*, 5426; *Chem. Commun.* **2017**, *53*, 7724; *Chem. Asian J.* **2017**, *12*, 1305; *Heterocycles* **2017**, *95*, 761; *J. Synth. Org. Chem. Jpn.* **2018**, *76*, 874; *ACS Catal.* **2018**, *8*, 5228; *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2751; *Chem. Eur. J.* **2019**, *25*, 9866; *Chem. Pharm. Bull.* **2020**, *68*, 299; *Adv. Synth. Catal.* **2020**, *362*, 1537; *Catalysts* **2020**, *10*, 860.