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Enantioselective Construction of Tetrasubstituted Carbon Stereocenters *via* Chiral Phosphoric Acid-Catalyzed Friedel–Craft Alkylation of Indoles with 5-Substituted Hydroxybutyrolactams

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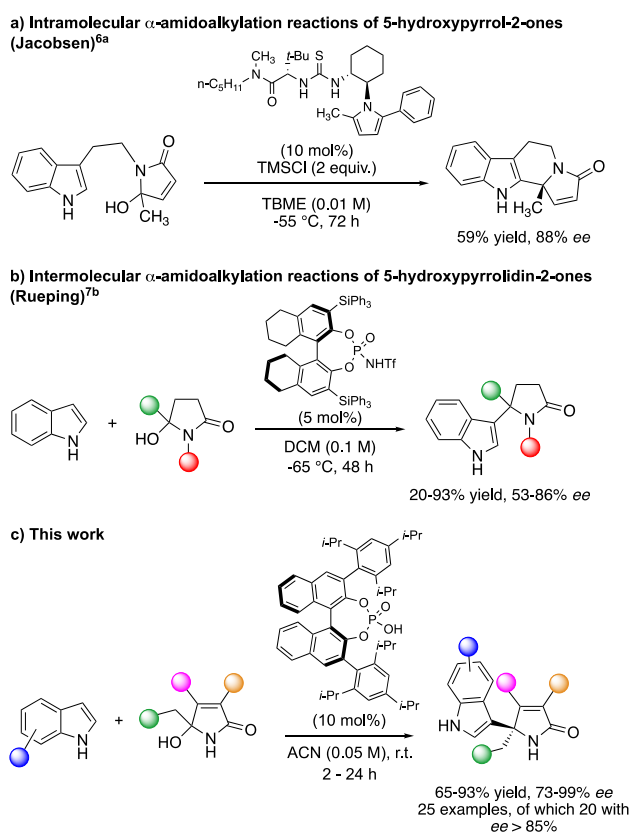
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KEYWORDS. Tetrasubstituted Stereocenter, Friedel-Craft Alkylation, Asymmetric Counteranion-Directed Catalysis, *N*-acyliminium ions, Hydroxybutyrolactams

ABSTRACT: The first intermolecular organocatalytic enantioselective addition of indoles to prochiral 5-membered cyclic *N*-acyliminium ions, generated from 5-hydroxy- α,β -unsaturated pyrrolidin-2-ones is reported hereinafter. The reaction proceeds smoothly with a range of 5-hydroxy-5-substituted- α,β -unsaturated pyrrolidin-2-ones and indoles using BINOL-derived phosphoric acid catalyst to afford α,β -unsaturated lactams embedding a tetrasubstituted stereogenic center in high yields and enantioselectivities.

The demand for enantiomerically pure compounds is constantly increasing since their properties are strongly linked to their stereochemistry. To access enantioenriched organic compounds, the overflying imagination of chemist has been tested allowing tactical strategies including *inter alia* enantioselective catalysis. Among the different concepts based on enantioselective catalysis, notably ion-pairing catalysis,¹ the use of enantiomerically pure counteranions proceeding through cationic intermediates (Asymmetric Counteranion-Directed Catalysis, ACDC) has proven successful.^{1,2} As cationic intermediates, prochiral 5-membered cyclic *N*-acyliminium ions (NAI) have provided a particularly well-suited application of this concept for the synthesis of naturally or synthetically occurring bioactive heterocyclic compounds. More specifically, chiral non-racemic 5-substituted- γ -lactams, could be accessed in a straightforward manner *via* inter- or intramolecular enantioselective α -amidoalkylation reactions using cyclic NAI ion intermediates generated *in situ* from 5-hydroxy- γ -lactams with either bifunctional chiral phosphoric acid or thiourea catalysts.³ In contrast to 3-hydroxyisoindolin-1-ones^{4,5} and 5-hydroxypyrrolidin-2-ones,^{6,7} 5-hydroxy- α,β -unsaturated pyrrolidin-2-ones are barely investigated to furnish the corresponding 5-substituted unsaturated lactams. To the best of our knowledge, only one example of an intramolecular enantioselective Pictet–Spengler type cyclisation promoted by a chiral thiourea catalyst has been reported by the group of Jacobsen.^{6a} This enantioselective α -amidoalkylation reaction allowed the preparation of tetrasubstituted carbon-containing unsaturated lactam in acceptable yield and satisfactory *ee* (Scheme 1a). In addition, although the intermolecular enantioselecti-



Scheme 1. Previous works for the intermolecular construction of tetrasubstituted stereocenter-containing pyrrolidinone-2,5-dione from 5-hydroxy- γ -lactams.

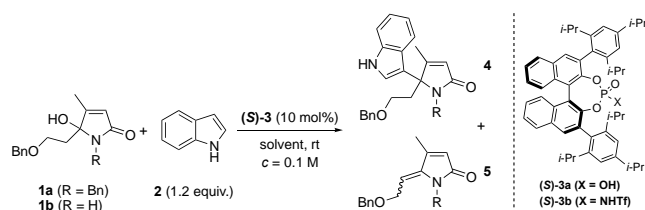
ve α -amidoalkylation reactions are quite deep-rooted for the construction of trisubstituted stereocenter-containing pyrrolidinones^{7a,c} with high enantiocontrol, the preparation of fully substituted stereogenic center remains more challenging. Rueping and Nachtsheim have shown that 5-indolyl-5-substituted γ -lactams could be prepared *via* a chiral *N*-triflylphosphoramidate-catalyzed Friedel–Craft alkylation, nonetheless, in both moderate yields and enantiocontrol (Scheme 1b).^{7b}

It is also worth noting that the scope of the inter- or intramolecular enantioselective α -amidoalkylation reactions is often hampered by the lack of versatility of the 5-hydroxy- γ -lactams since they are conventionally obtained by nucleophilic addition of either a hydride or alkyl, allyl or aryl Grignard reagents onto symmetrical pyrrolidine-2,5-diones. In this context, the development of novel catalytic methods for the enantioselective C–C bond formation with concomitant construction of a tetrasubstituted stereogenic centers is still a daunting challenge. Thereupon, we decided to investigate the enantioselective aza-Friedel–Crafts alkylation of indoles with various functionalized 5-hydroxy-5-methylsubstituted- α,β -unsaturated pyrrolidin-2-ones (5-hydroxy-5-methylsubstituted pyrrol-2-ones)⁸ for the chemo- and enantioselective preparation of valuable α,β -unsaturated lactams embedding a tetrasubstituted stereogenic center (Scheme 1c).

A preliminary evaluation of the catalyst was performed by reacting *N*-benzyl protected hydroxylactam **1a** and indole **2** (1.2 equiv.) in 1,2-DCE (0.1 M) at room temperature along with 3,3'-substituted BINOL-based Brønsted acid catalysts **3**. The desired reaction occurred in the presence of various chiral phosphoric acids providing mixture of the expected 5-indolyl-5-substituted- α,β -unsaturated pyrrolidin-2-one **4a** and the alkylidenebuterolactam **5a**, arising from an entropy-driven dehydration reaction. Whereas partial conversion, poor chemoselectivity and enantioselectivity were observed (see Supporting Information for a more detailed study), the use of sterically congested (*S*)-**3a** (Table 1, entry 1) gave **4a** with the best enantiocontrol (53%). Nevertheless, full conversion was never reached, even after 6 days and in quasi equimolar mixture with **5a**. More acidic Brønsted acid (*S*)-**3b** (Table 1, entry 2) allowed to increase the kinetic of the reaction at the expense of the enantiomeric excess. Further optimization of the reaction conditions with catalyst (*S*)-**3a** by changing the solvent, the concentration and the amount of the catalyst did not improve the catalytic efficiency and enantioinduction (see SI). Considering the envisaged activation mode operating through strict ion pair interactions of chiral phosphonate catalyst and cationic NAI intermediate appeared not efficient enough to improve enantioselectivity, we anticipated an activation strategy involving an additional hydrogen-bond that would favor the formation of a tight chiral ion-pair in the transition state. Indeed, previous studies have shown that the free N–H in 3-hydroxyisindolinones was crucial to obtain high enantiocontrol.^{5c-f,h} Therefore, *N*-unprotected hydroxylactam **1b** (R = H) was subjected to the aza-Friedel–Crafts reaction with indole **2** (Table 1, entry 3). As expected, we were delighted to obtain **4b** in 94% yield with higher *ee* value (74%), excellent chemoselectivity (ratio **4b** : **5b** = 1 : 0.03) and reaction time (8h). While a second screening of catalysts **3** did not improve the enantioselectivity, a subsequent survey of solvents (Table 1, entry 4 and see SI) unveiled promising results, with ethyl acetate and acetonitrile as best candidates (Table 1, entries 5 and 6). Regarding reactivity, chemo- and

enantioselectivity, acetonitrile was chosen as the solvent for the remainder of the study.

Table 1. Preliminary optimization of the reaction conditions.

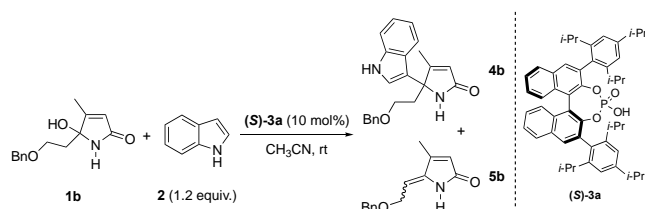


entry	R	(S)-3	solvent	time	conv (%) ^[a]	4 / 5	yield 4 (%)	ee (%)
1	Bn	(S)-3a	DCE	6d	72	1 / 1.08	30	53
2	Bn	(S)-3b	DCE	2d	100	1 / 0.2	80	20
3	H	(S)-3a	DCE	8h	100	1 / 0.03	94	74
4	H	(S)-3b	DCE	2h	100	1 / 0.02	98	20
5	H	(S)-3a	EtOAc	24h	100	1 / 0.06	94	91
6	H	(S)-3a	CH ₃ CN	5h	100	1 / 0.03	95	89

Conditions: Optimization study was conducted on 0.074 mmol of **1**.
^[a] Conversion determined by ¹H NMR.

After optimization of our catalytic system and solvent, further dilution of the reaction medium in acetonitrile was performed (Table 2, entries 1-3) and the best compromise between chemo-, enantio and efficiency was achieved by a concentration of 0.05M (Table 2, entries 2). In efforts to enhance enantioselectivity, the temperature was decreased to 0 °C, however affecting the performances. (Table 2, entry 4). Because water released during the formation of the NAI intermediate could have a detrimental impact on the reaction efficiency (reversible addition on NAI) and/or enantioselectivity by modifying the existent H-bond interactions, the reaction was carried out in the presence of molecular sieves as additives, fortunately with a similar outcome (Table 1, entry 10). Finally, conducting the reaction with one equivalent of indole **2** or with a decreased catalyst loading did not allow to observe improved results (Table 2, entries 6 and 7).

Table 2. Final optimization of the reaction conditions.

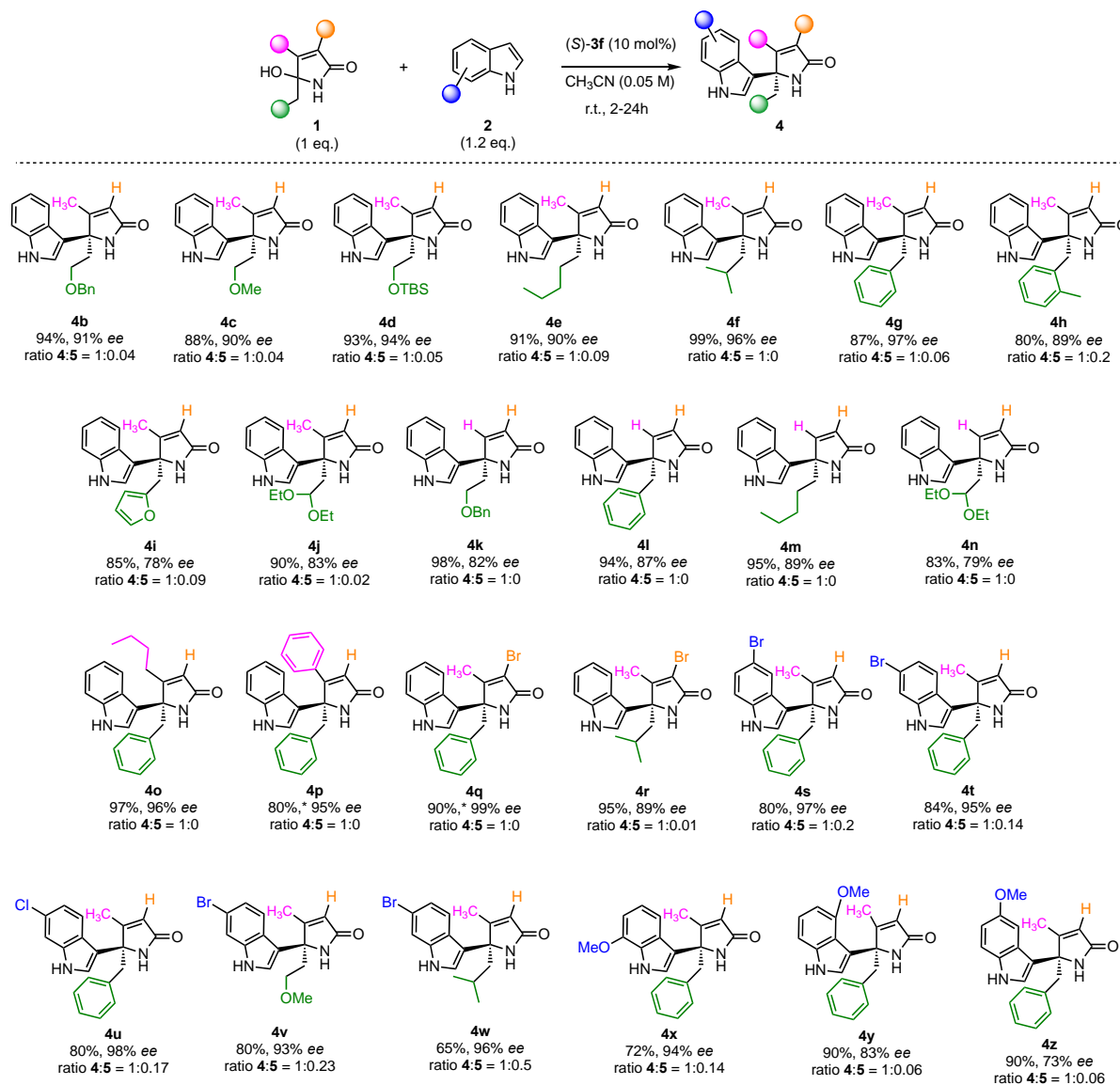


entry	c (M)	time	conv (%) ^[a]	4 / 5	yield 4 (%)	ee (%)
1	0.1	5h	100	1 / 0.03	95	89
2	0.05	6h	100	1 / 0.04	95	91
3	0.025	7h	100	1 / 0.06	94	91
4 ^[b]	0.05	3d	88	1 / 0.03	75	81
5 ^[c]	0.05	6h	100	1 / 0.03	94	91
6 ^[d]	0.05	16h	100	1 / 0.10	91	91
7 ^[e]	0.05	8h	100	1 / 0.04	96	88

Conditions: Optimization study was conducted on 0.074 mmol of **1b**.
^[a] Conversion determined by ¹H NMR. ^[b] Reaction was carried out at 0 °C.
^[c] With 4 Å molecular sieves as additives. ^[d] With 1 equiv. of **2**. ^[e] With 5 mol% of catalyst (*S*)-**3b**.

Subsequently, we next explored the scope and limitations of the reaction under the previous optimized conditions (Table 2, entry 2). We first examined the efficiency of this process by subjecting various 5-hydroxypyrrol-2-ones **1** bearing different substituents at the C5 position. Similar high enantioselectivities up to 94% were observed with methyl- and TBS protected alcohols **1c-d**. Both aliphatic and aromatic substituents were also tolerated providing the desired lactams **4e-i** in high yields and

enantiocontrols. It is noteworthy that while the highest value of 97% *ee* was observed with a C5 phenyl substituent, lower enantiocontrol (89% *ee*), was obtained with a *o*-tolyl substituent, probably due to steric hindrance. The lowest value of 78% *ee* was observed with a furanyl heteroaromatic group. Moreover, the reaction between indole and 5-diethoxyethyl-5-hydroxypyrrol-2-one bearing a sensitive ketal function, ran smoothly to afford the desired product **4j** in excellent yield (91%) and good enantioselectivity (83% *ee*).



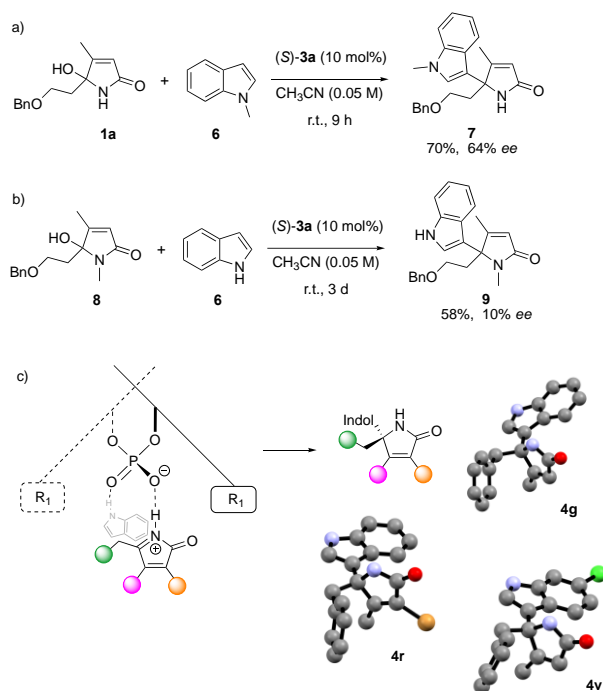
Scheme 2. Scope of the enantioselective Friedel–Craft alkylation of indoles with 5-substituted hydroxybutyrolactams

We next investigated the influence of the substituents at the C4 position. Without a C4 substituent, a slight drop of stereocontrol (82%–87% *ee*) was observed for the preparation of **4k-l**. However, the overall efficiency of the process was maintained for the preparation of **4m** and **4n**. Starting from 5-hydroxypyrrol-2-one bearing a C4 butyl or phenyl substituent, **4o** and **4p** were prepared with high enantioselectivities (96% and 95% respectively). In this last case, higher temperature (3 days at 60 °C)

favoured complete conversion of **1q** without any erosion of the enantiocontrol. Bromine atom at the C3 position, allowing further post-functionalization reactions, was also satisfactorily tolerated, giving rise to products **4q** and **4r** with excellent *ee* values (99 and 89%). As for **4q**, a temperature of 60 °C for 2 days was necessary to reach a total consumption of the starting material **1q**.

To further demonstrate the scope of this reaction, the reactivity of various substituted indoles **2** towards 5-hydroxypyrrol-2-ones **1c**, **1f** and **1g** was evaluated. As general trend, the reaction times were longer, and the efficiency of this enantioselective Friedel–Craft alkylation was sensitive to both the nature and the position of the substituents on the indole moiety. The C4-substitution of the indole core by a halogen atom is incompatible, delivering indeed alkylidenebuterolactam **5** as sole product in the crude ^1H NMR. In contrast, the corresponding alkylated products **4s–w** were obtained with excellent yields and enantioselectivities when 5-bromo, 6-bromo and 6-chloroindole were employed. Similarly, high enantiocontrol (94% *ee*) was observed when 7-methoxyindole reacted with **1g**. While tolerated, methoxy-substitutions at C4 or C5 positions resulted in lowering of the enantioselectivity for **4z** and **4aa** (83 and 73% respectively). The limitation of the reaction was reached with strong electron-withdrawing substituents such as 5-NO₂, 4-CN or 7-CHO on the indole **2**, giving alkylidenebuterolactams **5** as the exclusive outcome. It is worth noting that the reaction was scaled up to 1 mmol for the preparation of **4f** without any deterioration of both yield and enantioselectivity (95%, 95% *ee*).

As observed during the optimization of the reaction conditions, hydrogen-bonding interactions seemed to facilitate the Friedel–Crafts reaction of indole **2** with the *N*-acyliminium ion to furnish the enantioenriched products **4**. In order to verify the suggested activation mode, experiments with *N*-protected hydroxylactam **8** and *N*-protected indole **6** were performed under optimized reaction conditions (Schemes 3a and 3b). When *N*-methyl protected indole **6** reacts with *N*-unprotected hydroxylactam **1b**, product **7** is obtained in good yield (70%) and with a lower enantiocontrol (*ee* = 64 %). Worse, when *N*-methyl protected hydroxylactam **8** was engaged with *N*-unprotected indole **2b**, product **9** was obtained nearly as a racemate (*ee* = 10 %). These lower enantioselectivities indicate that BINOL-derived phosphoric acid **3a** would bind both reaction partners *via* their free NH bonds. Furthermore, X-ray crystal structure determination of **4g**,⁹ **4r**,¹⁰ and **4v**¹¹ were obtained, allowing to assign a (*R*) absolute configuration regarding these products and their analogs. This observation is in accordance with a Type II transition state model developed by Goodman for prediction of stereoselectivity (Scheme 3c).¹²



Scheme 3. Elucidation of the stereochemical induction

In conclusion, an enantioselective preparation of tetrasubstituted carbon stereocenters *via* chiral phosphoric acid-catalyzed Friedel–Craft alkylation of indoles with *in situ* generated cyclic 5-substituted *N*-acyl iminiums were developed. The reaction proceeded smoothly using a broad range of promising 5-hydroxy-5-methylsubstituted- α,β -unsaturated pyrrolidin-2-ones and indoles in high yields and enantioselectivities (up to 99% *ee*).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Synthesis procedures and ^1H and ^{13}C NMR spectra of each compound (file type, i.e., PDF)

CIF file of **4g**, **4r** and **4v** (file type, i.e., PDF)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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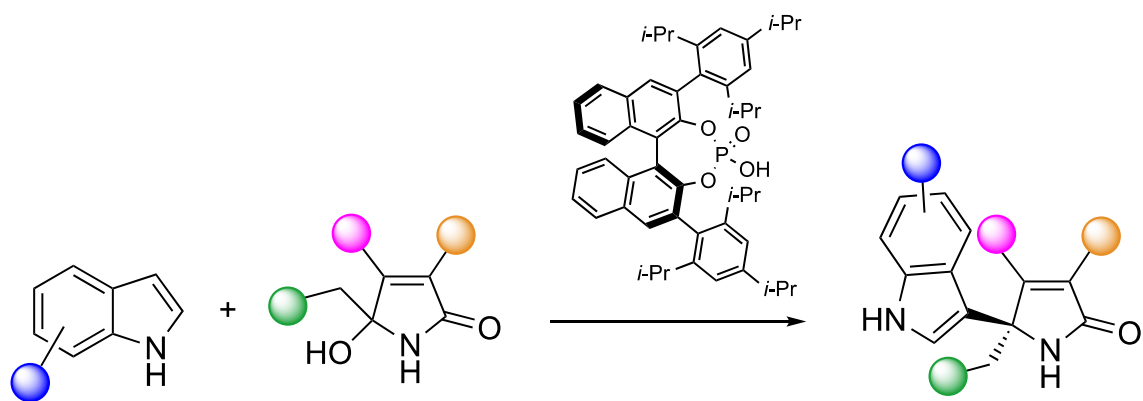
No competing financial interests have been declared.

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- ✓ *Tetrasubstituted stereocenters*
 - ✓ *High enantioselectivities*
 - ✓ *Molecular diversity*
 - ✓ *Scalable*
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