Organocatalysis

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Catalytic Enantioselective Intramolecular Aza-Diels–Alder Reactions**

*Chang Min, Chih-Tsung Lin, and Daniel Seidel**

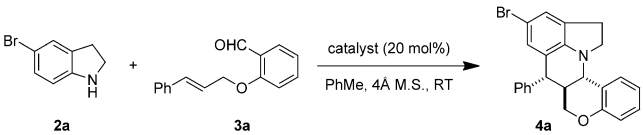
Abstract: *A readily available chiral Brønsted acid was identified as an efficient catalyst for intramolecular Povarov reactions. Polycyclic amines containing three contiguous stereogenic centers were obtained with excellent stereocontrol in a single step from secondary anilines and aldehydes possessing a pendent dienophile. These transformations constitute the first examples of catalytic enantioselective intramolecular aza-Diels–Alder reactions.*

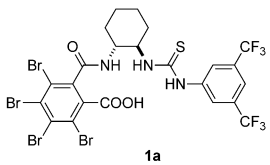
Intramolecular Diels–Alder (IMDA) reactions are among the most powerful tools for the rapid construction of polycyclic compounds and often generate multiple stereogenic centers in a single step.[1] Highly diastereoselective IMDA reactions are well developed and have been applied to the asymmetric synthesis of natural products and other bioactive materials.[1] Although far less developed than their diastereoselective variants, a number of elegant catalytic enantioselective IMDA reactions have been reported.[2] As a subclass of DA reactions, hetero-DA (HDA) reactions are widely used in the synthesis of biologically relevant heterocycles.[3] Over the past two decades, numerous reports on catalytic enantioselective intermolecular HDA reactions have appeared.[4] In stark contrast, their corresponding intramolecular variants remain rare and are largely limited to oxa-DA reactions.[5] To our knowledge, there has been no report on a catalytic enantioselective intramolecular aza-DA reaction.[6,7] Herein we report the first examples of such a process.

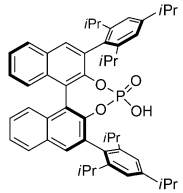
We recently introduced a new class of chiral Brønsted acid catalysts[8] (e.g., **1a**; for structure see Table 1) which comprise carboxylic acids[9] with a covalently connected anion-recognition site, specifically, a thiourea moiety.[10] These catalysts are thought to derive their acidity, at least in part, from stabilization of their respective conjugate bases through anion binding.[11–15] The catalyst **1a** was identified as being particularly effective and was applied to a catalytic enantioselective three-component Povarov reaction, a specific type of aza-DA reaction.[10a] Furthermore, **1a** was found to catalyze challenging Pictet–Spengler reactions.[10b] With regard to the Povarov process, a unique feature of our work was the use of indoline and other secondary-aniline-type amines. Iminium ions derived from these species lack acidic N-H protons, thus severely reducing the propensity for forming hydrogen-bond-stabilized ion pairs with the catalyst anion. In asymmetric phosphoric acid catalysis, such interactions have been invoked to play an important role in controlling the enantioselectivity of various transformations, including Povarov reactions. Possibly for this reason, catalytic enantioselective reactions with secondary amine substrates that involve intermediate iminium ions remain far less studied than the corresponding transformations with primary amines or preformed imines.[8]

For the purpose of developing the title transformation, 5-bromoindoline (**2a**) and the aldehyde **3a** were selected as model substrates (Table 1).[16] *O*-allylsalicylaldehyde derivatives closely related to **3a** have been used as starting materials for the synthesis of bioactive tetrahydrochromanoquinolines.[17] Achiral Lewis or Brønsted acids have been employed

Table 1: Evaluation of reaction conditions.[a]







Entry	Catalyst	Conc. [M]	*t* [h]	Yield [%]	d.r.	*ee* [%]
1	–	0.05	17	5	n.d.	–
2	TFA	0.05	17	14	1:1.3	–
3	**1a**	0.05	2	87	>20:1	97
4	**1b**	0.05	17	78	1:1	97/37
5	**1a**	0.1	2	80	>20:1	96
6	**1a**	0.025	17	38	11:1	91/38
7[b]	**1a**	0.05	12	91	>20:1	>99
8[c]	**1a**	0.05	72	63	10:1	94
9[c]	**1a**	0.1	72	69	7:1	91

[a] Reactions were performed with 0.2 mmol of **3a** and 1.2 equiv of **2a**. Yields correspond to chromatographically purified products. The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixtures. The *ee* values were determined by HPLC analysis; see the Supporting Information for details. [b] The reaction was performed at 0 °C. [c] With 10 mol% of **1a**. n.d. = not determined.

[*] C. Min, C. Lin, Prof. Dr. D. Seidel
Department of Chemistry and Chemical Biology
Rutgers, The State University of New Jersey
Piscataway, NJ 08854 (USA)
E-mail: seidel@rutchem.rutgers.edu
Homepage: http://seidel-group.com/

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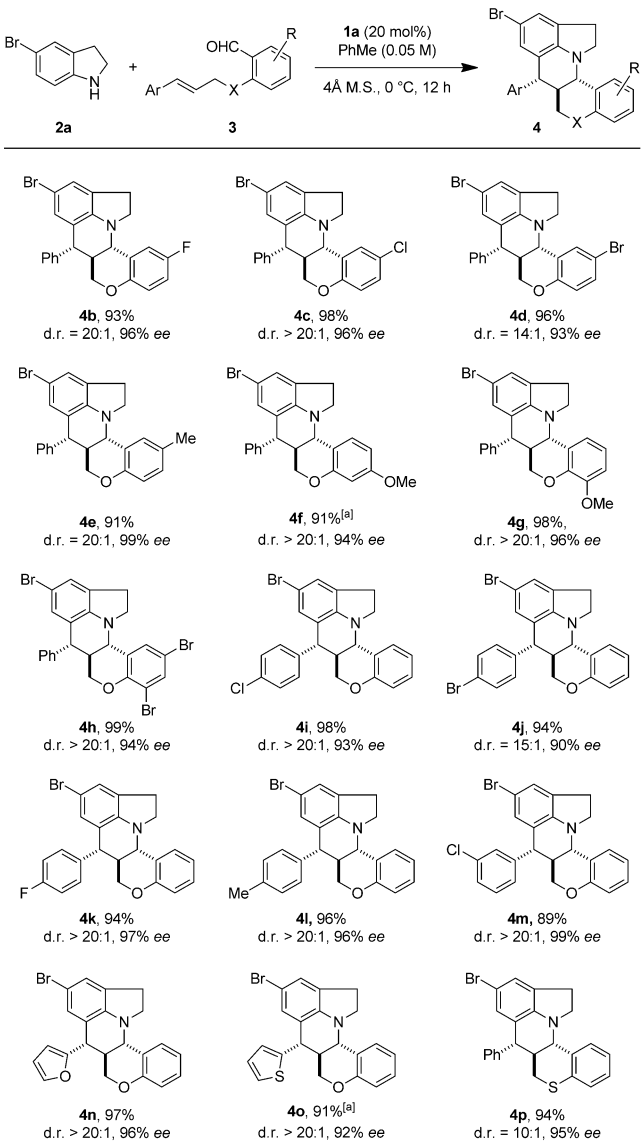
as catalysts/promoters in these intramolecular Povarov reactions, thus typically providing products such as **4a** as diastereomeric mixtures. When a reaction of **2a** and **3a** was conducted in the absence of catalyst, some background reactivity was noted (entry 1).[18] Surprisingly, the relatively strong carboxylic acid TFA, which is widely used to promote intramolecular Povarov reactions,[3b,7e,f] provided poor substrate conversion (entry 2). Gratifyingly, **1a** was found to be an excellent catalyst. After a reaction time of only two hours, **4a** was obtained in 87% yield and 97% *ee* as essentially a single diastereomer (entry 3). Interestingly, (*S*)-TRIP (**1b**), the most widely used chiral phosphoric acid catalyst,[8,19] showed comparable enantioselectivity while being substantially less active (entry 4). However, poor diastereoselectivity was observed, thus indicating vastly different modes of action for the two catalysts. Further evaluation of reaction conditions showed that a higher reaction molarity did not provide improvements (entry 5), and a lower substrate concentration led to a more sluggish reaction with loss of enantio- and diastereoselectivity (entry 6). Decreasing the reaction temperature to 0 °C further improved the yield of **4a** while raising the product *ee* value to more than 99% (entry 7).[20] A reduction in catalyst loading to 10 mol% led to a drop in reactivity and selectivity at different concentrations (entries 8 and 9).

As outlined in Scheme 1, *O*-allylsalicylaldehyde derivatives (**3**) with different substituents on the aldehyde phenyl ring reacted smoothly with **2a** to produce polycyclic heterocycles (**4**) in excellent yields and with high levels of diastereo- and enantioselectivity. With regard to the dienophile component, both electron-withdrawing and electron-donating groups on the phenyl group were tolerated. Heteroarenes such as furan and thiophene rings were also readily accommodated. Finally, the thiosalicylaldehyde-derived starting material **3p** was successfully transformed into the product **4p**. In this instance, the d.r. value was slightly eroded, but excellent yield and enantioselectivity were maintained.[21]

Next, the generality of the transformation was explored with regard to the amine component (Scheme 2). A number of indolines performed well. Tetrahydroquinoline was found to exhibit a lower level of reactivity, while providing the product **5f** with slightly reduced *ee* and d.r. values. Gratifyingly, *N*-methyl aniline, a representative acyclic secondary amine, engaged in the formation of the product **5g**. While a longer reaction time was required, this product was obtained with excellent d.r. and *ee* values, albeit in moderate yield. By employing a more electron-deficient acyclic substrate, namely 4-chloro-*N*-methylaniline, the corresponding product **5h** was obtained with excellent yield and stereoselectivity.

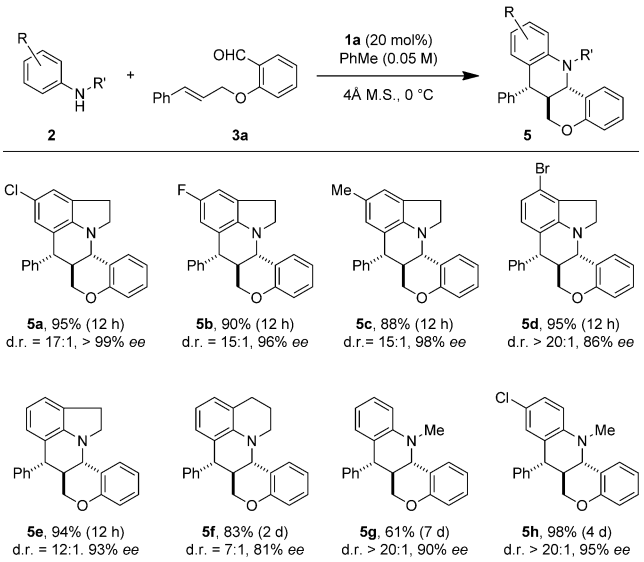
An unusual and interesting observation was made in the course of this study. While racemic samples of cycloaddition products were easily obtainable with TFA, diastereomeric mixtures of two products were typically obtained. In some cases, a third diastereomer was observed. This observation prompted us to evaluate racemic **1a** (*rac*-**1a**) as a catalyst to obtain diastereomerically enriched racemic products for HPLC analysis. Remarkably, *rac*-**1a** at a 20 mol% loading was nearly ineffective in accelerating the formation of *rac*-**4a**



Scheme 1. Aldehyde scope. Reactions were performed with 0.2 mmol of **3** and 1.2 equiv of **2a**. Yields correspond to chromatographically purified products. The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixtures. The *ee* values were determined by HPLC analysis; see the Supporting Information for details. [a] The reaction was run for 3 days.

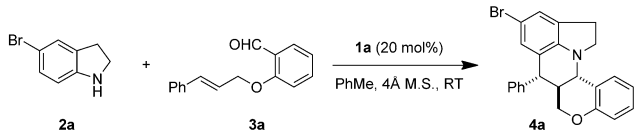
from **2a** and **3a**. Nonlinear effects were then evaluated in an effort to develop a more detailed understanding of this phenomenon (Table 2). Interestingly, the *ee* value of **4a** remained at a nearly identical level down to a catalyst *ee* value of only 10%. However, the reaction rate gradually slowed down with reduced catalyst *ee* values, with a substantial drop in reactivity being noted for a catalyst composition of less than 50% *ee*. Concurrent with the reduction in reaction rate, the diastereoselectivity diminished gradually.

The exceptionally pronounced nonlinear effect suggests a high degree of aggregation between *R*,*R*- and *S*,*S*-enantiomers. Importantly, aggregation of enantiomerically pure **1a** might also be relevant to the catalytic process. Such aggregation was previously noted in the solid-state structure of the



Scheme 2. Amine scope. Reactions were performed with 0.2 mmol of **3a** and 1.2 equiv of **2**. Yields correspond to chromatographically purified products. The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixtures. The *ee* values were determined by HPLC analysis; see the Supporting Information for details.

Table 2: Nonlinear effects study.[a]



Entry	**1a** (*ee* [%])	*t* [h]	Yield [%]	d.r.	*ee* [%]
1	100	2 h	87	>20:1	97/–
2	90	7 d	82	12:1	98/53
3	80	7 d	80	10:1	97/46
4	70	7 d	78	8:1	97/40
5	60	7 d	74	8:1	97/35
6	50	7 d	70	7:1	97/30
7	40	7 d	48	4:1	97/8
8	30	7 d	30	4:1	95/7
9	20	7 d	23	1.7:1	97/9
10	10	7 d	16	2:1	96/6
11	0	7 d	14	1:2	–
12	no catalyst	7 d	7	1:1	–

[a] Reactions were performed with 0.2 mmol of **3a** and 1.2 equiv of **2a** in the presence of **1a** with different *ee* values. Yields are those of chromatographically purified compounds. The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixture. The *ee* values were determined by HPLC analysis. Reactions in entries 7–12 did not reach full conversion of **3a** after 7 days.

tetrabutylammonium salt of (*R*,*R*)-**1a**.[10a] In fact, the observation that a reduction in reaction molarity (see entry 6 of Table 1) leads to a reduced diastereoselectivity is consistent with the notion that a (partially) de-aggregated catalyst anion might facilitate the formation of the minor product diastereomer.[22] Another case in point is the fact that the minor diastereomer of **4a** is obtained with appreciable *ee* value, meaning its formation cannot solely be attributed to a racemic background process.

In summary, we have reported highly enantio- and diastereoselective intramolecular Povarov reactions as the first examples of a catalytic enantioselective intramolecular aza-Diels–Alder reaction. A chiral conjugate-base-stabilized carboxylic acid catalyst was found to be uniquely effective in facilitating this transformation. Preliminary mechanistic studies revealed interesting catalyst aggregation phenomena which are the subject of ongoing investigations.

Experimental Section

General procedure: A flame dried vial was charged with aldehyde (0.2 mmol, 1 equiv), **1a** (34 mg, 0.04 mmol, 0.2 equiv), and powdered 4 Å M.S. (100 mg). Freshly distilled toluene (4 mL) was added and the resulting mixture was cooled to 0 °C over 10 min. The aromatic amine was then added (0.24 mmol, 1.2 equiv) and the reaction mixture was stirred at 0 °C. After the indicated reaction time, triethylamine (1 mmol, 0.14 mL) was added. The reaction mixture was warmed to RT, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated under reduced pressure and the crude product purified by flash chromatography.

Keywords: asymmetric catalysis · Brønsted acids · cycloaddition · ion pairs · organocatalysis

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[21] The starting material corresponding to **3a**, in which the oxygen linker was replaced with a methylene bridge, was equally reactive but provided product in racemic form (d.r. = 2:1).

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