Organocatalysis

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Catalytic Enantioselective Aza-Piancatelli Rearrangement

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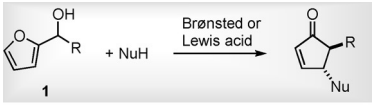
Abstract: *An efficient organocatalytic enantioselective aza-Piancatelli rearrangement is disclosed. The powerful process provides rapid access to valuable chiral 4-amino-2-cyclopentenone building blocks from readily available 2-furfurylcarbinols with excellent chemo-, enantio-, and diastereoselectivities under mild reaction conditions.*

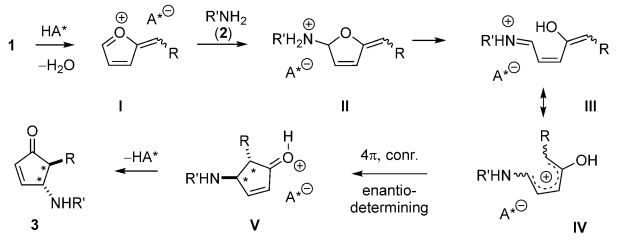
The Piancatelli rearrangement, first discovered in 1976,[1] represents one of most direct strategies to access highly functionalized 2-cyclopentenones, a family of valuable structural units (Scheme 1).[2,3] The power of this reaction has also been demonstrated in the synthesis of a range of useful molecules, including cyclopentenone prostaglandins.[3,4] As a result, in the past few decades the prototype reaction, initially with water as a nucleophile and promoted by a stoichiometric amount of acid, has been extended to a large family of catalytic transformations which are compatible with various internal and external nucleophiles, thus providing rapid access to more diversely substituted cyclopentenones (Scheme 1).[5–7] A range of catalytic systems, including those based on Lewis acids, such as $Dy(OTf)_3$, $Ca(NTf_2)_2$, and $In(OTf)_3$, have also been developed for these reactions. However, it is important to note that all these reactions are racemic. A catalytic enantioselective version of this reaction has remained as an unmet but highly desirable goal.



NuH: H_2O, alcohols, amines, arenes, etc.

Scheme 1. The general Piancatelli rearrangement.

Mechanistically, the Piancatelli rearrangement process involves a series of bond-formation and bond-cleavage steps together with ring-opening and ring-closing events (Scheme 2).[8] It is believed that the key 4π conrotatory electrocyclization step (**IV** to **V**) determines both diastereo- and enantioselectivity. However, the stereocontrol in this key step is expected to be challenging because of the limited defined stereochemistry in the linear precursor **IV**, as well as the elusive interaction with chiral metal/ligand systems.



Scheme 2. Proposed mechanism and asymmetric induction for the aza-Piancatelli rearrangement.

Nevertheless, intrigued by the presence of hydrogen-bonding sites in the key intermediate **IV** and the possible asymmetric induction by a chiral counter anion, we envisioned that chiral Brønsted acids might be able to render these reactions asymmetric.[9]

The aza-Piancatelli rearrangement, in which an amine is used as a nucleophile, was first used to test our hypothesis, partly because **IV** is an imine/iminium in nature, whose asymmetric induction by hydrogen bonding/counter anions has been established.[10] Another asset of this process is the valuable utility of the 4-amino-2-cyclopentenone products. They themselves and their simple derivatives are ubiquitous substructures in numerous natural products and pharmaceutically important molecules, such as stemonamine, homoharringtonine, etc.[11]

We began our study with 2-furfurylcarbinol (**1a**) as the representative substrate and aniline (**2a**) as the nucleophile. Chiral phosphoric acids were employed as catalysts in view of their superior performance in asymmetric induction of imines and iminiums.[10] Unfortunately, at room temperature, the representative catalyst (*R*)-**A1** (TRIP) could not promote the reaction between **1a** and **2a** in acetonitrile, which is the best solvent for most racemic examples (Table 1, entry 1).[5] The reaction could proceed slowly at 80 °C, but no desired product **3a** was observed. Indeed, the only product was **3a′**, which was formed by exocyclic addition of the amine nucleophile to the intermediate **I** (Scheme 2).[5k] We reasoned that the weak basicity of acetonitrile might reduce the catalyst activity by competitive binding. In fact, the same reaction in DCM proceeded with good conversion at room temperature, although the major product was still **3a′**. Encouragingly, the desired product **3a** was observed, albeit in low yield and with moderate enantioselectivity (Table 1, entry 2). Further screening of different phosphoric acid catalysts identified that (*R*)-**B4**[12] provided the best enantioselectivity (84 % *ee*) and a promising yield of **3a** (entry 7). Evaluation of other parameters indicated that the enantioselectivity could be further improved with DCE as the solvent at a 0.025 M concentration (entries 9–14). It is known that **3a′** can be

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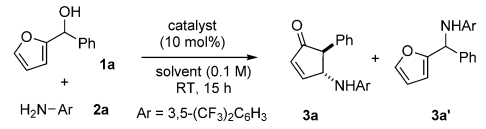
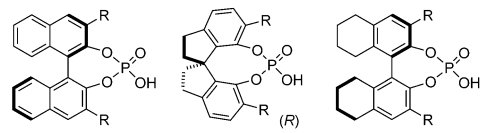
Table 1: Reaction optimization.[a]





A1: R = 2,4,6-$iPr_3C_6H_2$
A2: R = 1-pyrenyl
A3: R = 2,4,6-$Cy_3C_6H_2$

B1: R = 2,4,6-$iPr_3C_6H_2$
B2: R = 9-anthryl
B3: R = 9-phenanthryl
B4: R = 1-pyrenyl

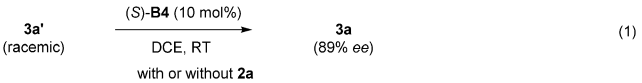
C1: R = 1-pyrenyl

Entry	Catalyst	Solvent	Conv. [%]	Yield [%]		*ee* [%]
				3a	**3a′**	**3a**
1	(*R*)-**A1**	MeCN	0	–	–	–
2	(*R*)-**A1**	DCM	80	3	77	34
3	(*S*)-**A2**	DCM	100	71	0	−66
4	(*S*)-**B1**	DCM	66	26	40	37
5	(*S*)-**B2**	DCM	100	26	74	46
6	(*R*)-**B3**	DCM	100	33	22	−68
7	(*S*)-**B4**	DCM	100	62	35	84
8	(*R*)-**C1**	DCM	100	70	0	73
9	(*S*)-**B4**	Et_2O	42	4	38	50
10	(*S*)-**B4**	EtOAc	76	9	67	58
11	(*S*)-**B4**	toluene	100	33	48	85
12	(*S*)-**B4**	DCE	100	49	33	86
13[b]	(*S*)-**B4**	DCE	100	36	0	86
14[c]	(*S*)-**B4**	DCE	100	44	55	90
15[c,d]	(*S*)-**B4**	DCE	100	74	14	90

[a] Yield and conversion were determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. The *ee* values were determined by chiral-phase HPLC. [b] Run at 0.2 M concentration. [c] Run at 0.025 M concentration. [d] Run for 64 h. DCE = 1,2-dichloroethane, DCM = dichloromethane.

possibly converted into **3a** via intermediate **I**.[5k] Indeed, the yield of **3a** was successfully improved by increasing the reaction time (entry 15).

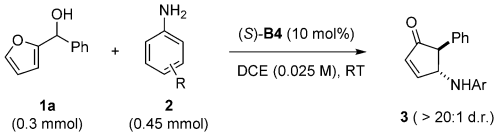
We carried out more studies to probe the reactivity and role of **3a′**. First of all, it was found that **3a′** was formed in essentially racemic form, even though a chiral catalyst was employed. Furthermore, when pure racemic **3a′** was subjected to the standard reaction conditions, with or without additional **2a**, **3a** was formed with enantioselectivity comparable to the case with **1a** [Eq. (1)]. These results proved that the formation of **3a′** is reversible, and **3a′** serves as an off-cycle reservoir for **I**. It is also consistent with the proposed mechanism which has a late enantiodetermining step (i.e., the 4π electrocyclization). Thus, the chirality of the preceding intermediates/substrates does not have direct influence on the stereochemical outcome. Moreover, subjection of **3a** to the standard reaction conditions did not lead to a change of its enantiopurity. Therefore, the product formation is irreversible under the given reaction conditions.



(1)

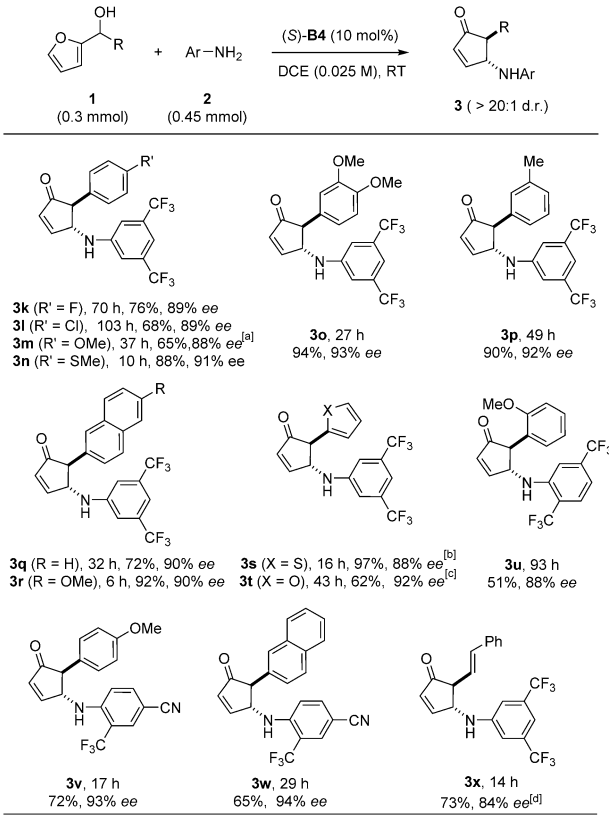
A range of variously substituted electron-deficient anilines and 2-furfurylcarbinols participated smoothly in the efficient intermolecular aza-Piancatelli rearrangement process under mild reaction conditions (Table 2 and Scheme 3). The corresponding 4-amino-2-cyclopentenones were formed with good to excellent enantioselectivities. In general the

Table 2: Scope with respect to anilines.[a]



Entry	R	*t* [h]	**3**	Yield [%]	*ee* [%]
1	3,5-$(CF_3)_2$	75	**3a**	66 (73)	90 (89)[b]
2[c]	2,5-$(CF_3)_2$	22	**3b**	83	93
3	2-CF_3-4-Cl	34	**3c**	92	89
4	2-CF_3-4-CN	48	**3d**	76	94
5	2-Br-4-CF_3	45	**3e**	76	85
6[d]	2-NO_2	31	**3f**	72	82
7	2-F-4-NO_2	42	**3g**	76	92
8	3-CF_3-4-NO_2	21	**3h**	92	90
9	2-Me-4-NO_2	26	**3i**	78	84
10	2-OMe-4-NO_2	31	**3j**	79	80

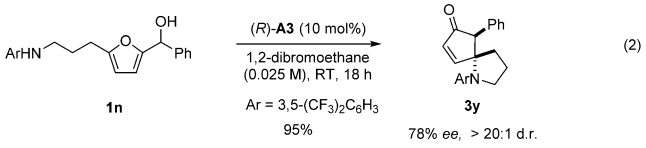
[a] Yield of isolated product. [b] Yield and *ee* values within parentheses are those for a reaction on 2 mmol scale. [c] 12:1 d.r. [d] 8:1 d.r.



Scheme 3. Scope with respect to the 2-furfurylcarbinols.[a] Presented yield is that of the isolated product. [a] Run at −20 °C. [b] 10:1 d.r. [c] 13:1 d.r. [d] 8:1 d.r.

diastereoselectivity was excellent, except for a few cases. The mild protocol is compatible with a range of functional groups. Heterocycles can also be incorporated in the products. Electron-rich or electron-neutral anilines can deactivate the catalyst. Therefore, no reaction was observed for them. Other nucleophiles, such as alcohols and arenes, did not afford the desired products. While alkyl-substituted or primary furfuryl alcohols (R = alkyl or H) exhibited no reactivity, we were pleased to find that an alkenyl-substituted one could lead to the desired product (**3x**). It is noteworthy that this protocol represents one of the most efficient and direct strategies to assemble these valuable enantioenriched 4-amino-2-cyclopentenones from achiral or racemic starting materials. Previous strategies either require a long synthetic sequence or kinetic resolution.[13] More importantly, the 2-furfurylcarbinol substrates can be easily prepared from the raw material furfural, a cheap and abundantly available commodity product from agricultural waste.[14]

We also examined the intramolecular version of this reaction using the substrate **1n** [Eq. (2)]. Under the standard reaction conditions, the reaction proceeded to form the desired product **3y** in quantitative yield, but in racemic form (0% *ee*). However, after optimization, we found that **A3** could catalyze this transformation with reasonably good enantioselectivity.

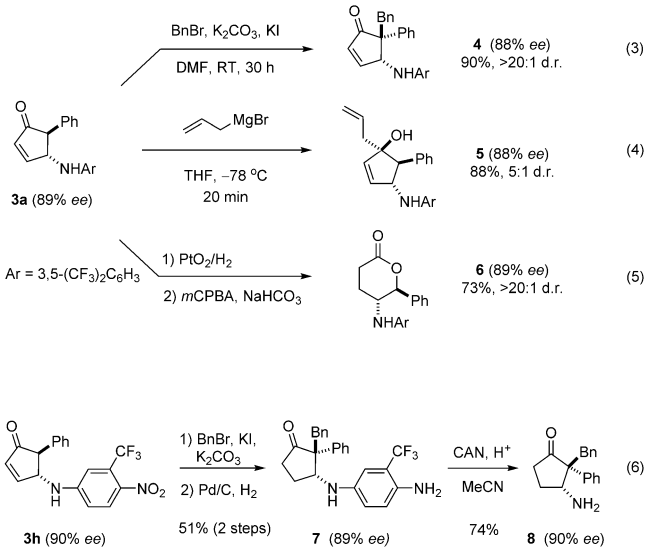


(2)

To demonstrate the utility of our protocol, we carried out some product derivatizations [Eqs. (3)–(5); DMF = *N*,*N*-dimethylformamide, *m*CPBA = *m*-chloroperbenzoic acid, THF = tetrahydrofuran]. For example, **3a** could undergo mild α-alkylation to form the cyclopentenone **4** bearing an α all-carbon quaternary stereocenter. Selective 1,2-addition of allyl Grignard reagent generated the tertiary alcohol **5** with high efficiency. Furthermore, after hydrogenation and Baeyer–Villiger oxidation, **3a** was smoothly converted into the γ-amino-δ-valerolactone **6**. Notably, in all these transformations, the high enantiopurity essentially remained without erosion. It is worth noting that previous assembly of these valuable chiral building blocks has not been so straightforward.

Finally, our protocol is not limited to access specific arylamino-substituted cyclopentenones. As shown in Equation (6), the *para*-nitro aryl group in product **3h** could be turned into an electron-rich aryl group by reduction. A subsequent oxidative cleavage successfully delivered the highly enantioenriched free amine **8**, which is poised for further transformations into other chiral amine derivatives, thereby representing an indirect expansion of the scope with respect to the nucleophile.[15]

In summary, we have developed the first catalytic enantioselective example of the Piancatelli rearrangement,



a large family of powerful transformations which provide rapid access to valuable cyclopentenone building blocks. With the proper choice of a chiral Brønsted acid catalyst, the intermolecular aza-Piancatelli reaction proceeds with excellent chemo-, enantio-, and diastereoselectivity under mild reaction conditions. It provides expedient access to a wide range of highly enantioenriched 4-amino-cyclopentenone products from readily available 2-furfurylcarbinols. These products can also be easily converted into other useful chiral molecules which are not previously generally or efficiently accessible. This process is also a demonstration of using chiral phosphoric acids for a new type of asymmetric reaction. Further investigations on other members of the Piancatelli rearrangement family are underway.

Acknowledgments

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[15] Without the first two steps, that is, with α,β-unsaturation and/or a hydrogen in the 5-position, the dearylation products seem to be unstable and easily decompose or epimerize.

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