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Chiral Phosphoric Acid-Catalyzed Enantioselective Aza-Friedel–Crafts Reaction of Indoles

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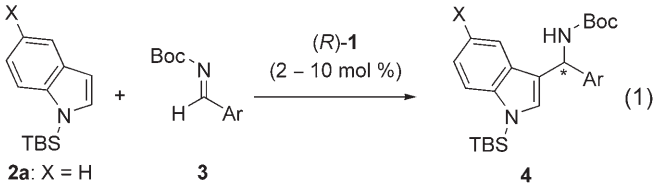
Abstract: A highly enantioselective 1,2-aza-Friedel–Crafts reaction of *N*-*tert*-butyldimethylsilylindole with *N*-*tert*-butoxycarbonyl aromatic imines is demonstrated using a BINOL-derived monophosphoric acid catalyst. The present approach provides efficient access to 3-indolylmethaneamines with aryl substituents in excellent enantioselectivities (up to 98% *ee*). An inversion in the sense of enantioselection was found between monophosphoric acid catalysts bearing different substituents introduced at the 3,3′-position of binaphthyl backbone. We also calculated the three-dimensional structure of the monophosphoric acid catalysts to speculate on the inversion of the stereochemical outcome.

Keywords: asymmetric catalysis; Brønsted acid; enantioselectivity; Friedel–Crafts reaction; organic catalysis; phosphoric acid

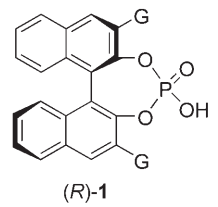
The enantioselective Friedel–Crafts (F–C) reaction *via* activation of electron-deficient multiple bonds is undoubtedly the most straightforward, atom-economical, and practical approach for the introduction of a chiral side chain to aromatic compounds.[1] Since the 1,4-F–C reaction of α,β-unsaturated carbonyl compounds with pyrrole derivatives catalyzed by small organic molecules, so-called organocatalysts,[2] was accomplished by MacMillan and co-workers,[3a] the development of organocatalytic F–C reactions has been a challenging topic of continued interest in synthetic organic chemistry. To date several efficient organocatalysts have been reported.[3,4] Our group has also demonstrated a highly enantioselective 1,2-aza-F–C reaction of *N*-protected imines with 2-methoxyfuran using the BINOL-derived monophosphoric acid **1a**[4a] as the chiral Brønsted acid catalyst.[4–7] Further applications of the chiral monophosphoric acid-catalyzed 1,2-aza-F–C reaction are desirable as it has the potential for high catalytic efficiency and enantioselectivity and should provide a diverse array of optically active arylmethaneamine derivatives. In particular, the 1,2-aza-F–C reaction of indoles is an attractive transformation towards enantioenriched 3-indolylmethaneamine derivatives.[3g,4c] These indolyl derivatives are widely identified as "privileged" structures among pharmacophores and are represented in thousands of natural isolates and many medicinal agents of versatile therapeutic action.[8] Herein we describe a highly enantioselective Friedel–Crafts reaction of indoles (**2**) with *N*-acyl aromatic imines (**3**) catalyzed by chiral monophosphoric acids (**1**) [Eq. (1)].[9] The present approach, which gives optically active 3-indolylmethaneamines substituted with an aromatic group, is a good complement to our previous method for preparing 3-



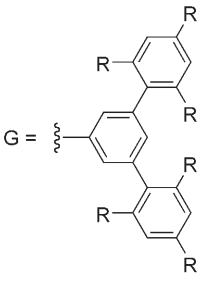
2a: X = H
b: X = Br
c: X = Me

3

4



(*R*)-**1**



(*R*)-**1a**: R = Me (G = HMT)
(*R*)-**1b**: R = H (G = TPH)

indolylmethaneamines with a variety of aliphatic substituents where a highly enantioselective F–C reaction of indoles with enecarbamates as electron-rich olefins catalyzed by chiral monophosphoric acid (**1**) was successfully developed.[4c] We also conducted computational analysis of the three-dimensional structure of the monophosphoric acid catalyst (**1**) to speculate about the activation mode of imines.

The initial reaction of the *N*-*tert*-butyldimethylsilyl (TBS)-protected indole (**2a**: X = H)[10] with *N*-Boc imne (**3a**: Ar = C_6H_5) was performed using the sterically hindered hexamethylterphenyl (HMT)-substituted catalyst [(*R*)-**1a**] as it was the most enantioselective and efficient catalyst for the 1,2-aza-F–C reaction of 2-methoxyfuran with *N*-Boc imines (**3**).[4a] The 1,2-aza-F–C reaction was carried out using 2 mol% of (*R*)-**1a**, and an enantioenriched F–C product (**4aa**: X = H, Ar = C_6H_5) was obtained in 68% yield [55% *ee* (*R*)] as shown in Table 1 (entry 1). However, catalysis of the reaction by (*R*)-**1a** was sluggish and the enantioselectivity was not sufficient despite thorough optimization of the reaction conditions. In order to enhance the catalytic activity and enantioselectivity, we derivatized the catalyst (**1**) by changing the substituent (G) attached at the 3,3′-position of the binaphthyl backbone. Screening of the substituents revealed that terphenyl (TPH) groups (**1b**) were effective for the present enantioselective F–C reaction, albeit affording only moderate enantioselectivity (67% *ee*) (entry 2). It is noteworthy that, for enantioselective catalysis by (*R*)-**1b**, the stereochemical outcome of (*S*)-**4aa** was opposite to that observed for the catalysis by (*R*)-**1a**, where the methyl groups were removed from the HMT substituent without any change to the terphenyl skeleton. To our delight, further optimization of the catalysis by (*R*)-**1b** (entries 3–6) markedly improved the enantioselectivity from 67% *ee* to 96% *ee*; in the optimum reaction conditions the temperature was set to −40 °C and the solvent was 1,1,2,2,-tetrachloroethane (entry 6). The reaction can be performed using a low loading of the catalyst (2 mol%) and the use of only a slight excess of imines (**3**) to *N*-TBS indoles (**2**) is possible to afford the corresponding products (**4**) in good chemical yield[11] without formation of the bisindolyl by-product[12] under the optimized conditions.

Table 1. Enantioselective 1,2-aza-Friedel–Crafts reaction of *N*-TBS indole (**2a**) with *N*-Boc imine (**3a**) catalyzed by chiral monophosphoric acid (*R*)-(**1**) [Eq. (1): X = H, Ar = C_6H_5].[a]

Entry	**1**	Solvent	Temperature	Time [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	$CHCl_3$	r.t.	12	68	55 (*R*)
2	**1b**	$CHCl_3$	r.t.	12	79	67 (*S*)
3	**1b**	$CH_3C_6H_5$	r.t.	12	84	60 (*S*)
4	**1b**	Et_2O	r.t.	24	37	47 (*S*)
5	**1b**	$CHCl_3$	−40 °C	24	74	93 (*S*)
6	**1b**	$(CHCl_2)_2$	−40 °C	24	85	96 (*S*)

[a] All reactions were carried out with 0.002 mmol of (*R*)-**1** (2 mol%), 0.1 mmol of *N*-TBS indole (**2a**), and 0.11 mmol of *N*-Boc imine (**3a**: Ar = C_6H_5) in 1 mL of the indicated solvent.

[b] Isolated yield.

[c] Enantiomeric excess was determined by chiral HPLC analysis. See Supporting Information for details. The absolute stereochemistry was estimated from X-ray single crystal analysis of **4aj**.

With the optimized reaction conditions in hand, the scope of the enantioselective 1,2-aza-F–C reaction was investigated. Representative results of (*R*)-**1b**-catalyzed reactions are summarized in Table 2. The electronic nature of the indole ring did not compromise the catalytic activity and the corresponding F–C products (**4**) were obtained in good yield while maintaining a high enantioselectivity (entries 1 and 2). High enantioselectivities were also observed for a series of aromatic imines examined (entries 3–17), but the position of the substituent on the aromatic ring exhibited a strong impact on the catalytic activity. For example, the *ortho* substituents retarded the reaction markedly (entries 3 and 7) and an increase in catalyst loading was required to obtain the desired product (**4ab**) in an acceptable yield (entries 4 and 8). Although *meta* substitution resulted in slightly lower enantioselectivities (entries 5, 9, 11), **1b** exhibited excellent performance in reaction with *para*-substituted aromatic imines (**3**) bearing a broad range of substituents irrespective of their stereoelectronic properties (entries 6, 10, 12–17).

To understand the inversion in the sense of stereochemical outcome observed in the catalysis between (*R*)-**1a** and (*R*)-**1b**, we conducted a computational study[6d] of the 3D-structures of the catalysts (**1**) at the B3LYP/6-31G** level of theory. The optimized 3D-structures of (*R*)-**1b** and (*R*)-**1a** are shown in Figure 1.[13] We speculate that the observed inversion of the enantioselectivity would be attributed to the accessibility of the reactants to acidic site of the catalyst (**1**). As depicted in Figures 1a and 1b, the TPH substituents of (*R*)-**1b** were arranged somewhat parallel on the top and bottom sides of the phosphoric acid moiety making a reaction pocket, in what we termed the "front" of the acid moiety. It is likely that the catalyst (*R*)-**1b** provides just enough space to construct a transient structure of the F–C reaction in front of the acidic moiety (Figure 1a). In contrast, for the sterically demanding HMT substituents of (*R*)-**1a** (Figures 1c and 1d), the *ortho* methyl substituents force the mesi-

Table 2. Enantioselective aza-Friedel–Crafts reaction of *N*-TBS indole (**2**) with a series of *N*-Boc imine derivatives (**3**) catalyzed by (*R*)-**1b**.[a]

Entry	**1b** [mol%]	**2**	**3** (Ar)	**4**	Yield [%][b]	*ee* [%][c]
1	2	**2b**	**3a**: C_6H_5	**4ba**	83	94
2	2	**2c**	**3a**	**4ca**	79	91
3	2	**2a**	**3b**: 2-$CH_3C_6H_4$	**4ab**	16	90
4	10	**2a**	**3b**	**4ab**	65	91
5	3	**2a**	**3c**: 3-$CH_3C_6H_4$	**4ac**	76	94
6	3	**2a**	**3d**: 4-$CH_3C_6H_4$	**4ad**	91	96
7	2	**2a**	**3e**: 2-FC_6H_4	**4ae**	20	82
8	10	**2a**	**3e**	**4ae**	81	83
9	2	**2a**	**3f**: 3-FC_6H_4	**4af**	77	89
10	2	**2a**	**3g**: 4-FC_6H_4	**4ag**	82	97
11	2	**2a**	**3h**: 3-ClC_6H_4	**4ah**	73	87
12	2	**2a**	**3i**: 4-ClC_6H_4	**4ai**	89	98
13	2	**2a**	**3j**: 4-BrC_6H_4	**4aj**	80	98 (*S*)[d]
14	2	**2a**	**3k**: 4-$CF_3C_6H_4$	**4ak**	80	93
15	2	**2a**	**3l**: 4-$MeOC_6H_4$	**4al**	85	89
16	3	**2a**	**3m**: 4-*i*-PrC_6H_4	**4am**	81	97
17	3	**2a**	**3n**: 4-PhC_6H_4	**4an**	76	97

[a] All reactions were carried out with (*R*)-**1b**, 0.1 mmol of *N*-TBS indole (**2**), and 0.11 mmol of *N*-Boc imine (**3**) in 1 mL of 1,1,2,2-tetrachloroethane at −40 °C for 24 h.
[b] Isolated yield.
[c] Enantiomeric excess was determined by chiral HPLC analysis. See Supporting Information for details.
[d] The absolute stereochemistry of **4aj** was determined to be *S* by X-ray single crystal analysis.

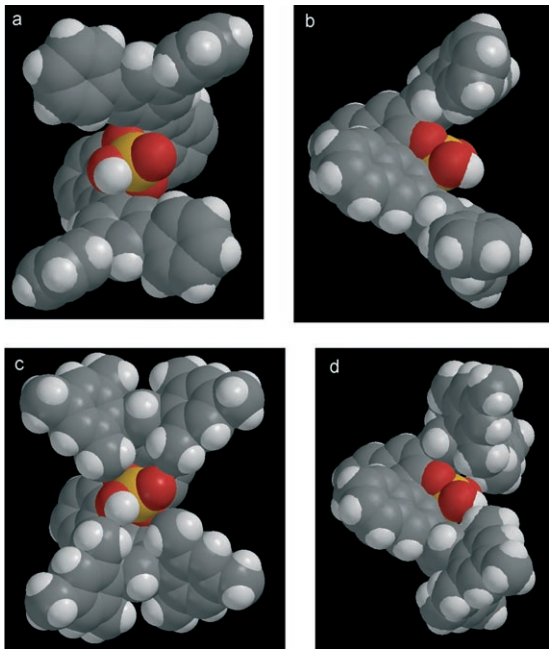


Figure 1. 3D-structures for the optimized geometries (at the B3LYP/6-31G** level of theory) of (*R*)-**1**. P tan, O red, C gray, H white. (**a**, *top left*) Front view of (*R*)-**1b** (G = TPH). (**b**, *top right*) Side view of (*R*)-**1b**. (**c**, *bottom left*) Front view of (*R*)-**1a** (G = HMT). (**d**, *bottom right*) Side view of (*R*)-**1a**.

tyl ring to be perpendicular to the basal phenyl moiety and thus causing the "front" side of the acidic moiety to be congested. Hence, formation of the transient structure of the F–C reaction would be prevented on the "front" side of the acidic moiety (Figure 1c). As a result, we speculate that the catalytic reaction would proceed avoiding the sterically congested front side of the acidic moiety.[13]

In conclusion, a highly enantioselective 1,2-aza-F–C reaction of indole with aromatic imines is demonstrated using a BINOL-derived monophosphoric acid catalyst [(*R*)-**1b**]. The present approach provides efficient access to enantioenriched 3-indolylmethaneamines with aryl substituents (up to 98% *ee*) and effectively complements our previous method that afforded aliphatic group-substituted 3-indolylmethaneamines *via* activation of enecarbamates. Furthermore, a large excess of reactants was not necessary to avoid the formation of the undesirable bisindolyl by-product. Further studies to elucidate the inversion in the sense of the enantioselectivities are in progress in our laboratory.

Experimental Section

Typical Procedure for Aza-Friedel–Crafts Reaction of *N*-TBS-Protected Indole (2) with *N*-Boc Protected Aldimines (3)

To a dried test tube was weighed the binaphthol monophosphoric acid [(*R*)-**1a**; 1.95 mg, 2 mol%, 0.002 mmol] and the atmosphere was replaced with nitrogen. The catalyst was dissolved in 1,1,2,2-tetrachloroethane (1 mL). *N*-Boc pro-

tected imine (**3a**: Ar = C_6H_5, 22.6 mg, 1.1 equivs., 0.11 mmol) and *N*-TBS protected indole (**2a**: X = H, 23.1 mg, 0.10 mmol) were introduced at −40 °C in this order. The resulting solution was stirred for 24 h under these conditions, then the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (1 drop). The reaction mixture was poured on silica gel column and purified by column chromatography (hexane/EtOAc = 12/1–8/1 as eluent). The F–C product (**4aa**) was obtained in 85% yield as a white solid. The enantiomeric excess was determined by HPLC analysis.

Acknowledgements

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[10] The F–C reaction of *N*-unprotected indole with *N*-Boc imine (**3a**) took place immediately at room temperature without any catalysts. To suppress this uncatalyzed pathway in the F–C reaction, we initially explored *N*-protected indoles (**2**). After several trials, the *tert*-butyldimethylsilyl group found to be the best, where a trace amount of the F–C product was obtained without cata-

lysts even at room temperature for 24 h; see Supporting Information for details.

[11] In previous reports of the enantioselective organocatalytic approach for 1,2-aza-F–C reaction of *N*-sulfonylimines, at least 10 mol% of catalyst loading and an excess of indoles (more than 2 equivalents) were required for the reaction to proceed effectively; see refs.[3g,9]

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[13] We also examined computational analysis of hydrogen-bonding pairs of the catalysts (**1**) with *N*-Boc imines (**3**) at the B3LYP/6–31G** level of theory. See Supporting Information for details.

