Organic LETTERS

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Fiaud's Acid: A Brønsted Acid Catalyst for Enantioselective Friedel–Crafts Alkylation of Indoles with 2-Alkene-1,4-diones

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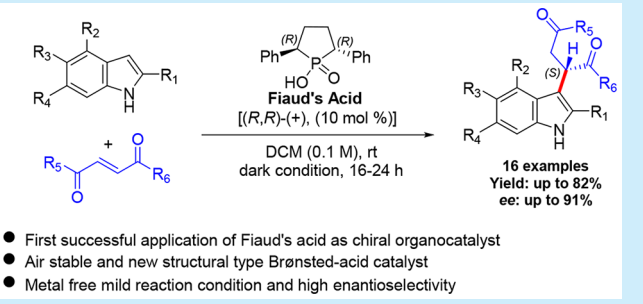
Supporting Information

ABSTRACT: Fiaud's acid (*trans*-1-hydroxy-2,5-diphenylphospholane 1-oxide), a phospholane-based phosphinic acid, is introduced as an efficient chiral Brønsted acid catalyst that mediates the asymmetric Friedel–Crafts alkylation of indoles with 2-butene-1,4-diones. With a catalyst loading of 10 mol %, the reaction proceeded smoothly to afford 2-(indol-3-yl)butane-1,4-diones in high yield (up to 82%) and high enantioselectivity (up to 91% ee, one such product showed enhanced ee of 98% after recrystallization). The reaction conditions are sufficiently mild to tolerate sensitive functionality at room temperature and are therefore suitable for the synthesis of complex targets.



Enantioselective organic transformation by organocatalysts is a thriving area of research throughout the world.[1] The advent of organocatalysis brought with it the prospects of ease of operation, lower toxicity of the catalysts, inexpensive operations, no sensitivity toward moisture and air, reductions in chemical waste, and the potential for new lines of academic thought and investigation.[2] On the application of chiral Brønsted acids of BINOL-phosphate type for a wide range of asymmetric reactions,[3] different groups have reported applications for various reactions such as Mannich-type,[4] Friedel–Crafts,[5] hydrogenation,[6] hetero-Diels–Alder,[7] multicomponent cascade reactions,[8] and metal co-catalyzed reactions[9] as well. Considering the widespread usage of chiral Brønsted phosphoric acids in asymmetric organic transformations, a major limitation comes from the continuous use of the highly successful BINOL-phosphoric acids, which are considered to be privileged structures. However, structural modifications of the backbones of the BINOL are fundamentally limited. It is desirable to have a choice of other fundamental structural types of chiral phosphoric acid with alternative backbones.

We have found Fiaud's acid to be a potential structural type that can be used in asymmetric catalysis (Figure 1). To the best of our knowledge, this phosphinic acid (**A**), known as Fiaud's acid, has never been used as a chiral Brønsted acid catalyst. Recently, Fiaud and co-workers reported the synthesis and resolution of *rac*-2,5-diphenylphospholanic acid (±**A**), which is a valuable building block for synthesizing 2,5-diphenylphospholane-containing chiral ligands for asymmetric transition-metal catalysis.[10,11] It occurred to us that the C_2-symmetric phosphinic acid structure of this compound might also be suited for applications as a chiral Brønsted acid catalyst where

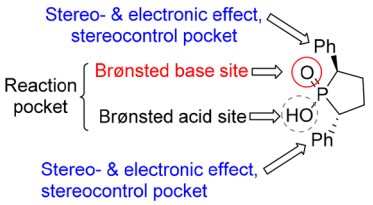


Figure 1. Stereo and electronic properties of chiral Fiaud's acid (*R*,*R*)-(+)-**A**.

the steric and electronic properties of the 2,5-diarylphospholane backbone could potentially be fine-tuned to accommodate the specific requirements of the reaction and the substrate.[10] Fiaud's phosphine ligand has already proved successful in various synthetic applications.[11] One of us has recently reported an asymmetric catalytic synthesis of Fiaud's acid from thiophene, which can potentially be extended to variable 2,5-diarylphospholane structures, and thus opens the way for structural fine-tuning (Figure 2).[12] However, the fundamental ability of Fiaud's acid to act as a chiral Brønsted acid catalyst remains unproven. We now wish to report a proof of concept study where we show that Fiaud's acid is a new structural type of chiral Brønsted acid that can catalyze the Friedel–Crafts alkylation of indoles with 2-butene-1,4-dione acceptors in very high (>90% ee) enantioselectivity.

To investigate our hypothesis, the catalytic property of Fiaud's acid [(*R*,*R*)-**A**] was tested in the model alkylation

Received: May 8, 2017

DOI: 10.1021/acs.orglett.7b01383
Org. Lett. XXXX, XXX, XXX–XXX

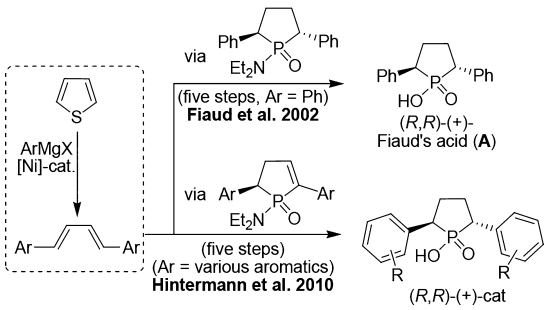
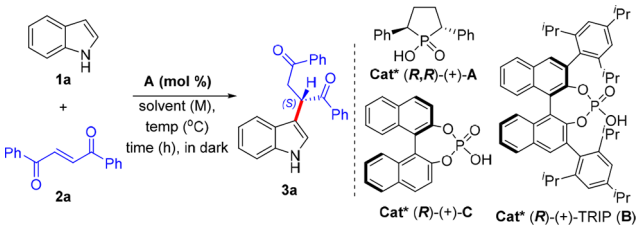


Figure 2. Synthesis of 2,5-diarylphospholanes from 1,4-diaryl-1,3-butadienes.

reaction of indole (**1a**) with (*E*)-1,4-diphenyl-2-butene-1,4-dione (**2a**). Using 10 mol % of [(*R*,*R*)-**A**] in dry toluene (0.1 M) at room temperature afforded the corresponding alkylated product **3a** in satisfactory yield (67%) with moderate, but notable, enantiopurity (Table 1, entry 1). The choice of solvent proved to have an important influence on both the rate and enantioselectivity of the reaction; dichloromethane was the preferred solvent, but other halogenated hydrocarbons were equally well suited (entries 1−5). Polar solvents proved unsatisfactory (entries 6−10). Prolonging the reaction time over the standard 22 h did not increase the product yield (entry 2 vs 11, 12). Counterintuitively, increasing the concentration reduced the conversion (entry 2 vs 13, 14), which appears to be a consequence of the limited solubility of the catalyst that effectively increases the substrate/catalyst ratio. Indeed, a higher conversion was achieved under more dilute conditions (entry 15). No improvement of enantioselectivity was attained by lowering the reaction temperature to 0 °C (entry 16); the yield of product dropped, which can be ascribed both to slower kinetics and poor solubility of the catalyst. At room temperature, a catalyst loading of 10 mol % gave the best results with respect to yield and ee (entry 1 vs 17, 18). Interestingly, when the reaction was carried out in daylight, a fraction (2−5 mol %) of the starting material (*E*)-**2a** was isomerized to (*Z*)-**2a**, which did not respond to alkylation.[13] In order to avoid this transformation, reactions were typically performed in the dark. From the results of Table 1, the optimal reaction conditions for the model transformation were established to involve 10 mol % of (*R*,*R*)-(+)-**A** as catalyst in dry dichloromethane at a concentration of 0.1 M at ambient temperature (~25 °C) over 22 h in the dark.[14] To demonstrate the advantage of the present catalytic system, the reaction was carried out using well-known BINOL-derived phosphoric acid catalysts like (*R*)-TRIP[15] (**B**, entry 19) and 3,3′-BINOL-phosphoric acid (**C**, entry 20). Both catalysts afforded the desired product **3a** in moderate yield and poor enantiopurity. Thus, the present catalytic system has the advantage of improved enantioselectivity.

Table 1. Optimization of Asymmetric Friedel−Crafts Alkylation by Using Fiaud's Acid and Known BINOL-phosphoric Acids as Catalysts[a]



entry	cat. (mol %)	solvent (M)	time (h)	yield[e] (%)	ee[f] (%)
1	10	toluene (0.1)	24	67	51
2	10	DCM (0.1)	22	72	59
3	10	$CHCl_3$ (0.1)	24	63	22
4	10	PhCl (0.1)	24	64	47
5	10	1,2-DCE (0.1)	24	66	48
6	10	CH_3OH (0.1)	24	22	12
7	10	dioxane (0.1)	24	NR	ND
8	10	CH_3CN (0.1)	24	NR	ND
9	10	THF (0.1)	24	NR	ND
10	10	DMF (0.1)	24	NR	ND
11	10	DCM (0.1)	36	75	57
12	10	DCM (0.1)	42	75	56
13	10	DCM (0.2)	22	45	58
14	10	DCM (0.5)	22	39	47
15	10	DCM (0.05)	22	70	58
16[b]	10	DCM (0.1)	22	39	60
17	5	DCM (0.1)	22	44	57
18	20	DCM (0.1)	22	74	60
19[c]	10	DCM (0.1)	22	60	32
20[d]	10	DCM (0.1)	22	48	04

[a]Reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol), and catalyst (*R*,*R*)-**A** in the given solvent at the indicated concentration at room temperature (~25 °C) in the dark. [b]Reaction temperature 0 °C. [c](*R*)-TRIP (**B**) was used as a chiral Brønsted acid catalyst. [d](*R*)-BINOL-phosphoric acid (**C**) was used as a chiral Brønsted acid catalyst. [e]Yields were determined by ^{1}H NMR analysis using 1,2-dichloroethane as internal standard. NR= no reaction. [f]Determined from chiral HPLC analysis. ND = not determined.

With these optimized reaction conditions in hand, the scope of the reaction was explored by using various indole derivatives (**1a−l**) and electrophiles **2a−e** (Scheme 1). The alkylation products **3a−e** and **3h−o** were obtained in high yields (67−82%) with moderate-to-high enantioselectivity (39−91% ee). The substituent at the C2 position of indole had an important influence on the reaction efficacy; sterically demanding substituents induced excellent enantioselectivity (up to 91% ee) with a significant improvement in the yield of the corresponding products (**3a−e**). Not unexpectedly, the electron-deficient substrates **1f** and **1g** did not respond to alkylation with **2a**. The effect of indole C4, C5, and C6 substitution (substrates **1h−l**) was found to not significantly alter the ee, but it did lower the enantiomeric excess of the respective reaction products **3h−l**. Under optimized conditions, (*R*)-TRIP (**B**) as catalyst instead of Fiaud's acid for the reaction of C2-substituted indole **1d** with **2a** afforded compound **3d** in comparable enantioselectivity (84% ee, Scheme 1) and yield.

Considering the synthetic versatility of the resulting adducts, our next attempt was focused on expanding the reaction scope toward other prochiral electrophiles (**2b−e**). The reaction proceeded well with diaryl as well as alkylaryl enediones. The unsymmetrical (*E*)-1-phenylpent-2-ene-1,4-dione (**2c**) reacted with 2-phenylindole (**1c**) regioselectively, providing the alkylated product **3n** in moderate yield (67%) and enantioselectivity (65% ee). Even the less activated acceptor methyl (*E*)-4-oxo-4-phenylbutenoate (**2d**) reacted with 2-phenyl indole (**1c**) to regioselectively afford **3o**. On the other hand, the dialkyl enedione 1,2-diacetylethylene (**2e**), in which the *trans*-alkene unit is flanked by two acetyl groups, proved inactive under the above reaction conditions. In contrast to indoles, carbazoles proved unreactive as nucleophiles. The

DOI: 10.1021/acs.orglett.7b01383
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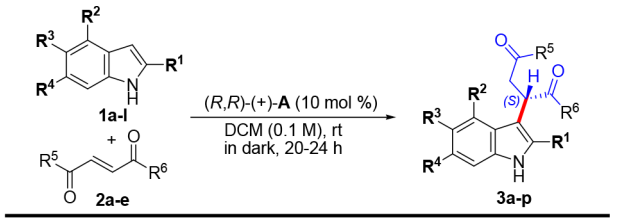
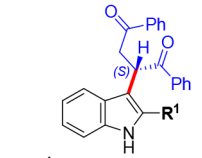
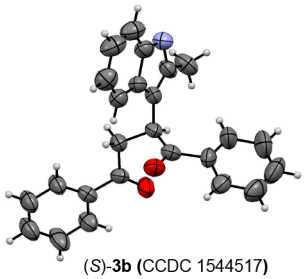
Scheme 1. Fiaud's Acid (*R,R*)-(+)-A-Catalyzed Asymmetric Friedel–Crafts Alkylation of Substituted Indoles with *trans*-Enediones[a,b]

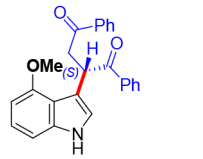




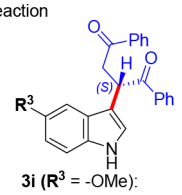
3a (**R**[1] = -H): 67% (ee = 59%), 22 h
3b (**R**[1] = -Me): 72% (ee = 85%), 22 h[c]
3c (**R**[1] = -[t]Bu): 80% (ee = 91%), 22 h
3d (**R**[1] = -Ph): 78% (ee = 82%), 22 h
[60% (ee = 84%), 22 h][d]
3e (**R**[1] = -βNapth): 82% (ee = 84%), 22 h[e]
3f (**R**[1] = -COOEt): no reaction
3g (**R**[1] = -2-Pyridyl): no reaction



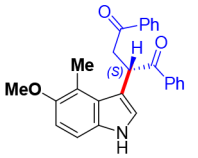
(*S*)-**3b** (CCDC 1544517)



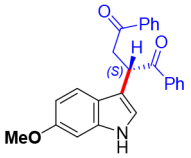
3h: 71% (ee = 39%), 20 h



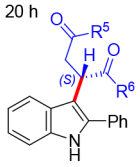
3i (**R**[3] = -OMe): 72% (ee = 48%), 20 h
3j (**R**[3] = -Br): 70% (ee = 47%), 20 h



3k: 69% (ee = 40%), 24 h



3l: 73% (ee = 45%), 22 h



3m (**R**[5], **R**[6] = -*p*BrC$_6$H$_4$): 78% (ee = 86%), 22 h
3n (**R**[5] = -Ph, **R**[6] = -Me): 67% (ee = 65%), 22 h
3o (**R**[5] = -Ph, **R**[6] = -OMe): 70% (ee = 68%), 22 h
3p (**R**[5], **R**[6] = -Me): no reaction

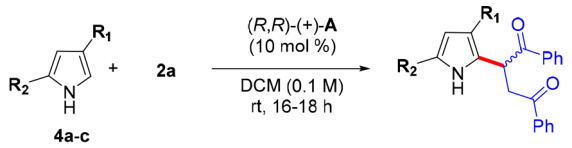
[a]Isolated yields are given. [b]Enantiomeric excess determined by chiral HPLC. [c]98% ee after recrystallization. [d](*R*)-TRIP (**B**) was used as catalyst. [e]94% ee after recrystallization.

combinations of *β*-nitrostyrene with 2-phenyl indole gave the expected product (**3q**), but as a racemic mixture (see the Supporting Information). The major enantiomers of all isolated products were found to have the (*S*)-configuration with a positive sign for the optical rotation and positive CD (λ_{max} = 345 nm).[16,17] The relative configuration, optical rotation, and sign of the CD spectra were further compared with the literature report.[16]

In another extension of the asymmetric catalytic Friedel–Crafts alkylation with Fiaud's acid as catalyst, pyrroles **4a–c** were reacted with *trans*-1,2-dibenzoylethylene (**2a**) under the reaction conditions already used for indoles (Scheme 2). Although the reactions proceeded smoothly to give the alkylated pyrroles **5a–c** in >70% yield, unexpectedly, these products were obtained as racemic mixtures.

We anticipated that the indole NH unit, which is capable of hydrogen bonding to a phosphoryl oxygen (P═O) of the catalyst, plays a key role in defining the enantioselectivity of the Friedel–Crafts alkylation. To test this hypothesis, the standard reaction was repeated with two *N*-methylated indoles (**1m,n**),

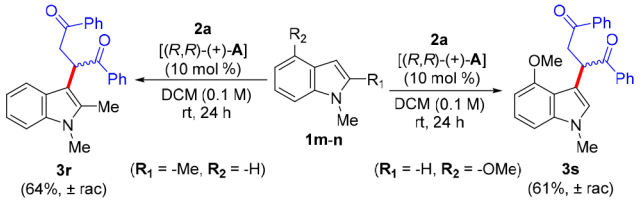
Scheme 2. Fiaud's Acid Catalyzed Asymmetric Friedel–Crafts Alkylation of Substituted Pyrroles 4a–c with *trans*-Enedione 2a



5a (**R**$_1$ = **R**$_2$ = -H): 70%, (±)-*rac*
5b (**R**$_1$ = -H, **R**$_2$ = -Et): 78%, (±)-*rac*
5c (**R**$_1$ = -Me, **R**$_2$ = -Me): 81%, (±)-*rac*

and while the expected reaction products (**3r** and **3s**) were obtained, they were found to be racemic (Scheme 3), strongly suggesting that free indole N–H is essential for enantiocontrol in this transformation.

Scheme 3. Friedel–Crafts Alkylation of *N*-Methylindoles 1m,n



The good ee's of the products in Scheme 1 indicate the preferential approach of indole to the *Re* face of the enedione (*E*)-double bond if (*R,R*)-**A** is the catalyst. On the basis of the investigation of the reaction conditions and the substrate diversity, we postulate a mechanism for this enantioselective transformation (Figure 3). The nucleophilicity of the indole

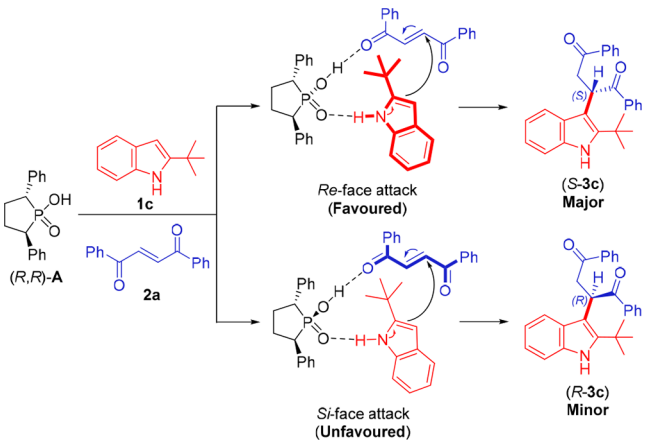


Figure 3. Suggested mechanism for the Fiaud's acid catalyzed Friedel–Crafts alkylation of 2-*tert*-butylindole (**1c**) with (*E*)-1,4-diphenyl-2-butene-1,4-dione (**2a**).

derivative is fostered through hydrogen bonding between indole-NH and phosphoryl oxygen (P═O) of the phosphinic acid (**A**). Simultaneously, the Brønsted acidic hydroxyl group (P–OH) of **A** increases the electrophilicity of the enedione acceptor via hydrogen bonding to a carbonyl group. Both substrates are thus involved in a spatially defined interaction with the catalyst in the transition state. The lack of hydrogen bonding of *N*-methylated indoles **3r,s** to the phosphoryl oxygen

DOI: 10.1021/acs.orglett.7b01383
Org. Lett. XXXX, XXX, XXX–XXX

of **A** disrupts this cyclic transition state, and consequently, racemic products are obtained.

In summary, we have reported for the first time the successful use of Fiaud's phosphinic acid as a new structural type of chiral Brønsted acid catalyst in an asymmetric Friedel–Crafts alkylation of indoles with 2-ene-1,4-diones to deliver products in good yield (up to 82%) and high enentioselectivities (up to 91% ee, which could be improved to 98% ee after recrystallization). The enantiomerically enriched indoles synthesized by the process are potential intermediates for natural product synthesis and for the synthesis of biologically active compounds. Further applications of 2,5-diaryl-substituted phospholane-based phosphinic acids for various asymmetric transformations are currently being pursued in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Representative experimental procedures, spectroscopic data, ^{1}H and ^{13}C NMR spectra, and chiral HPLC profiles for all synthesized molecules, crystallographic data for **3b**, (*R,R*)-(+)-**A**, and (*S,S*)-(−)-**A** are provided. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01383.

Representative experimental procedures, spectroscopic data, ^{1}H and ^{13}C NMR spectra, and chiral HPLC profiles for all synthesized molecules; crystallographic data for **3b**, (*R,R*)-(+)-**A**, and (*S,S*)-(−)-**A** (PDF)

X-ray crystallographic data for compound **3b** (CIF)

X-ray crystallographic data for compound (*R,R*)-(+)-**A** (CIF)

X-ray crystallographic data for compound (*S,S*)-(−)-**A** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project was funded by SERB, New Delhi, India (EEQ/2016/000605). P.J. thankfully acknowledges DAAD, Bonn, Germany, for the award of a DAAD fellowship under the reinvitation program-2013 for a visit to the laboratory of L.H. S.C. thankfully acknowledges UGC, New Delhi, India, for the award of research fellowships. We thank Mr. Sandip Kundu for data collection and Dr. Ramalingam Natarajan for his help in determination of structures (X-ray single-crystal), Dr. Tapas Sarkar (NMR), and Mr. Diptendu Bhattacharya (HRMS) for instrumental analysis.

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(13) In order to confirm the unreactivity of (*Z*)-**2a** in the Friedel–Crafts alkylation with indoles, a test reaction was performed with (*Z*)-**2a** and 2-*tert*-butylindole (**1c**) following the optimized reaction conditions. After 24 h, only 5% of desired **3c** was obtained (determined by crude NMR analysis using toluene as an internal standard), and the remaining mixture was found to be unreactive starting materials. For detailed NMR analysis, see the Supporting Information.

(14) A significant difference in enantiomeric excess (ee dropped to 9%) was found when commercially available nondried DCM was used instead of dry DCM.

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(17) CCDC 1544517 (**3b**), CCDC 919165 [(*R,R*)-**A**], and CCDC 919163 [(*S,S*)-**A**]; see the Supporting Information for details.

DOI: 10.1021/acs.orglett.7b01383
Org. Lett. XXXX, XXX, XXX–XXX