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Novel brønsted acid-catalyzed Michael-type Friedel-Crafts reactions of indoles and acetalization of aldehydes

Wei Zhou [a,b], Li-Wen Xu [a,b,*], Lei Yang [a,b], Pei-Qing Zhao [a,b], Chun-Gu Xia [a,b,*]

[a] *State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, PR China*
[b] *Graduate School of the Chinese Academy of Sciences, Beijing, PR China*

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Abstract

The first example of 2,6-pyridinedicarboxylic acid (PDA)-catalyzed organic reactions was developed in this article. The special bifunctional brønsted acid could be used in the chemoselective acetalization of aldehydes for preparation of corresponding acetals in excellent yields, and the Michael-type Friedel-Crafts reactions of indoles with α,β-unsaturated enones were also promoted by the same catalyst efficiently.

Keywords: Brønsted acid; Friedel-Crafts; Conjugate addition; Organocatalysis

1. Introduction

Since recognized as a major concept, organic catalysis has attracted much attention and has been applied extensively in non-asymmetric and asymmetric reactions due to its determined scientific significance and its huge potential in organic chemistry [1]. Recent years, inspired by the interesting work of List, Miller, and other chemists [2], organocatalyzed reactions have enjoyed a renewed progress. The design and use of organic catalysts similar to amino acid with two distinct functionalities are becoming more popular. Although organic molecules, such as amino acid, peptide, carbene, urea, phase-transfer agents, etc., have been used as catalysts in carbon–carbon and carbon–heteroatom bond-forming reactions [3], they are still limited to certain one or some reactions. So searching of new organic catalysts universally used in versatile reactions is highly desirable [4].

In this article, we described the remarkable catalytic activity of a novel organic brønsted acid in versatile reactions, Friedel-Crafts reaction and acetalization of aldehyde.

2. Experimental

2.1. General considerations

All reagents and solvents were used directly without purification. Flash column chromatography was performed over silica (100–200 mesh). ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 400 and 100 MHz, respectively, and were referenced to the internal solvent signals. GC-MS, Agilent 6890N GC/5973N MS, HP-5MS. IR spectra were recorded using a FTIR apparatus. Thin layer chromatography was performed using silica; gel F_{254} TLC plates and visualized with ultraviolet light.

2.2. Representative procedure for the Michael-type Friedel-Crafts reaction

2,6-Pyridinedicarboxylic acid (PDA) (0.1 mmol) was added to the solution of enone (1 mmol) and indole (1.1 mmol) in anhydrous MeOH (3 ml). After the mixture was stirred for 24 h at room temperature, the solvent was removed and the residue was purified by column chromatograph (silica gel, EtOAc-petro ether, 1:5) to give the pure product. All the compounds were identified by GC-MS and usual spectral methods.

2.2.1. ***3a***

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.97$ (bs, 1 H), 7.93 (d, $J = 7.2$ Hz, 2 H), 7.53 (t, $J = 7.4$ Hz, 1 H), 7.40–7.44 (m, 3 H),

* Corresponding authors. Tel.: +86 931 4968129; fax: +86 931 8277088.
E-mail addresses: licpxulw@yahoo.com (L.-W. Xu), cgxia@lzb.ac.cn (C.-G. Xia).

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7.35 (d, J = 7.2 Hz, 2 H), 7.23–7.31 (m, 3 H), 7.14 (q, J = 7.2, 7.2 Hz, 2 H), 7.01 (t, J = 7.4 Hz, 1 H), 6.96 (s, 1 H), 5.07 (t, J = 7.2Hz, 1 H), 3.81 (dd, J = 6.8, 6.8 Hz, 1 H), 3.72 (dd, J = 7.6, 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.6, 144.2, 137.0, 136.6, 133.0, 128.6, 128.4, 128.1, 127.8, 126.6, 126.3, 122.1, 121.4, 119.5, 119.4, 119.2, 111.1, 45.2, 38.1; IR (KBr): 3462, 3078, 3056, 3024, 1669, 1597, 1580, 1490, 758, 746, 703, 692 cm^{-1}; MS (EI): m/z = 325.

2.2.2. ***3b***

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (bs, 1 H), 7.92 (d, J = 7.6 Hz 2 H), 7.54 (t, J = 7.0 Hz, 1 H), 7.42 (t, J = 6.8 Hz 2 H), 7.38 (d, J = 8.4 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.24–7.28 (m, 2 H), 7.18–7.22 (m, 2 H), 7.15 (t, J = 7.6 Hz, 1 H), 7.01 (t, J = 7.4 Hz, 1 H), 6.97 (s, 1 H), 5.03 (t, J = 7.2 Hz, 1 H), 3.79 (dd, J = 6.8, 6.4 Hz, 1 H), 3.68 (dd, J = 8.0, 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 142.7, 136.9, 136.6, 133.2, 131.9, 129.2, 128.6, 128.5, 128.0, 126.4, 122.3, 121.3, 119.5, 119.4, 118.9, 111.2, 44.9, 37.5; IR (KBr): 3398, 3084, 3056, 3026, 1681, 1596, 1579, 1489, 820, 768, 746, 689 cm^{-1}; MS (EI): m/z = 359.

2.2.3. ***3c***

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.97 (s, 2 H), 7.55 (t, J = 7.2 Hz, 1 H), 7.38–7.46 (m, 3 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.26 (s, 1 H), 7.20–7.24 (m, 1 H), 7.08–7.17 (m, 3 H), 7.02 (t, J = 7.6 Hz, 2 H), 5.54 (t, J = 7.4 Hz, 1 H), 3.80 (dd, J = 8.8, 8.8 Hz, 1 H), 3.68 (dd, J = 6.4, 6.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.0, 141.6, 136.9, 136.6, 133.6, 133.0, 129.8, 129.0, 128.6, 128.2, 127.6, 126.9, 126.7, 122.2, 122.0, 119.5, 119.5, 117.8, 111.1, 44.2, 34.9; IR (KBr): 3375, 3056, 1677, 1619, 1595, 1577, 768, 754, 742, 685 cm^{-1}; MS (EI): m/z = 359.

2.2.4. ***3d***

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (bs, 1 H), 7.92 (d, J = 8.0 Hz, 2 H), 7.52(t, J = 7.2 Hz, 1 H), 7.39–7.44 (m, 3 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.25 (s, 1 H), 7.22–7.24 (m, 1 H), 7.13 (t, J = 7.6 Hz, 1 H), 7.00 (t, J = 7.6 Hz, 1 H), 6.96 (s, 1 H), 6.78 (d, J = 7.2 Hz, 2 H), 5.00 (t, J = 7.4 Hz, 1 H), 3.78 (dd, J = 6.8, 6.4 Hz, 1 H), 3.73 (s, 3 H), 3.68 (dd, J = 8.0, 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 158.0, 137.2, 136.7, 136.3, 132.9, 128.7, 128.5, 128.1, 126.6, 122.1, 121.3, 119.7, 119.6, 119.4, 113.8, 111.1, 55.2, 45.4, 37.5; IR (KBr): 3422, 1670, 1250, 1032 cm^{-1}; MS (EI): m/z = 355.

2.2.5. ***3e***

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (bs, 1 H), 7.88–7.92 (m, 2 H), 7.41 (d, J = 8.0 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.21–7.25 (m, 2 H), 7.12 (t, J = 7.6 Hz, 1 H), 6.99 (t, J = 7.4 Hz, 1 H), 6.96 (s, 1 H), 6.88 (d, J = 9.6 Hz, 2 H), 6.77 (d, J = 8.0 Hz, 2 H), 4.99 (t, J = 7.4 Hz, 1 H), 3.83 (s, 3 H), 3.73 (s, 3 H), 3.72 (dd, J = 7.6, 6.8 Hz, 1 H), 3.62 (dd, J = 8.0, 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 163.4, 157.9, 136.6, 136.4, 130.4, 130.2, 128.7, 126.6, 122.1, 121.3, 119.8, 119.6, 119.3, 113.7, 113.7, 111.1, 55.4, 55.2, 45.0, 37.6; IR (KBr): 3431, 3063, 3048, 3011, 2953, 2834, 1662, 1598, 1571, 1510, 1459, 1335, 1254, 1177, 1129, 1024, 846, 828, 818, 767, 743 cm^{-1}; MS (EI): m/z = 385.

2.2.6. ***3f***

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (t, J = 7.8 Hz, 1 H), 7.94 (d, J = 8.0 Hz, 2 H), 7.43 (d, J = 8.0 Hz, 1 H), 7.23–7.28 (m, 3 H), 7.14 (t, J = 7.2 Hz, 2 H), 7.02 (t, J = 7.2 Hz, 1 H), 6.92 (s, 1 H), 6.79 (d, J = 8.4 Hz, 2 H), 4.97 (t, J = 7.4 Hz, 1 H), 3.77 (dd, J = 6.0, 5.6 Hz, 1 H), 3.73 (s, 3 H), 3.70 (dd, J = 7.6, 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5, 158.0, 150.0, 141.4, 136.6, 135.6, 128.9, 128.6, 126.3, 123.6, 122.1, 121.3, 119.8, 119.3, 119.3, 113.8, 111.2, 55.1, 45.7, 37.6; IR (KBr): 3419, 1695, 1511, 1346, 1248, 1044 cm^{-1}.

2.2.7. ***3g***

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (bs, 1 H), 7.92 (d, J = 8.8 Hz, 2 H), 7.43 (d, J = 8.4 Hz, 1 H), 7.29–7.35 (m, 3 H), 7.24 (t, J = 7.4 Hz, 2 H), 7.14 (q, J = 6.8, 8.0 Hz 2 H), 6.97–7.03 (m, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 5.06 (t, J = 7.4 Hz, 1 H), 3.84 (s, 3 H), 3.76 (dd, J = 7.2, 6.8 Hz, 1 H), 3.66 (dd, J = 8.0, 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.0, 163.4, 144.4, 136.6, 130.4, 128.4, 127.8, 126.7, 126.2, 122.1, 121.4, 119.6, 119.3, 113.7, 111.1, 55.4, 44.8, 38.4; IR (KBr): 3432, 1665, 1265, 1023 cm^{-1}; MS (EI): m/z = 355.

2.2.8. ***3h***

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (bs, 1 H), 7.90 (d, J = 8.8 Hz, 2 H), 7.42 (d, J = 8.0 Hz, 1 H), 7.21–7.29 (m, 3 H), 7.08–7.12 (m, 1 H), 6.97–7.08 (m, 3 H), 6.93 (d, J = 8.4 Hz, 2 H), 5.00 (t, J = 7.4 Hz, 1 H), 3.82 (s, 3 H), 3.73 (dd, J = 7.2, 6.8 Hz, 1 H), 3.61 (dd, J = 8.0, 7.6 Hz, 1 H), 2.25 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 163.4, 141.3, 136.6, 130.4, 129.0, 127.6, 127.4, 126.6, 122.7, 122.0, 121.4, 119.8, 119.5, 119.2, 113.7, 111.1, 55.4, 44.9, 38.9, 20.9; IR (KBr): 3412, 1673, 1259, 1028 cm^{-1}; MS (EI): m/z = 369.

2.2.9. ***3i***

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, J = 7.6 Hz, 2 H), 7.79 (bs, 1 H), 7.48 (t, J = 7.2 Hz, 1 H), 7.34–7.43 (m, 3 H), 7.16–7.27 (m, 5 H), 6.97–7.08 (m, 2 H), 5.04 (t, J = 7.0 Hz, 1 H), 3.89 (m, 1 H), 3.87 (m, 1 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.8, 142.7, 137.0, 135.4, 133.0, 131.7, 131.5, 128.9, 128.5, 128.3, 128.0, 127.2, 120.8, 119.3, 118.9, 113.2, 110.5, 43.4, 36.2, 12.0; IR (KBr): 3410, 3350, 1671, 1597, 1456, 1261, 1206, 740, 692 cm^{-1}; MS (EI): m/z = 373.

2.3. Representative procedure for the acetalization of aldehydes

PDA catalyst (0.2 mmol) was added to a solution of aldehyde (2 mmol) in alcohol. The mixture was stirred at room temperature for 24 h, the yield was determined by GC. All the products in Table 2 are known compounds, and the structure was determined by GC-MS (Agilent 6890N GC/5973N MS, HP-5MS).

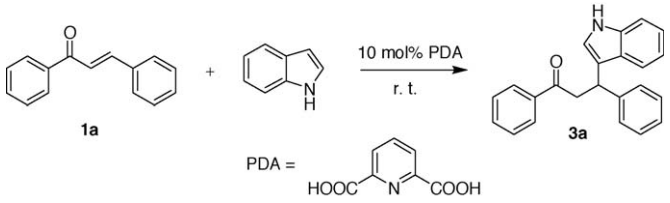
3. Results and discussion

After the pioneering study by Charles Friedel and James M. Crafts, the Friedel-Crafts reaction has become one of the most powerful carbon–carbon bond-forming processes in organic synthesis [5]. Among the Friedel-Crafts reactions, the Michael-type Friedel-Crafts reaction of indoles to electron-deficient olefins or α,β-unsaturated enones is a widely investigated process because it is involved in the total synthesis of a class of bioactive indole alkaloids known as hapalindoles and other 3-substituted indoles. In the past decade, stoichiometric amounts of Lewis acids promoted Friedel-Crafts procedures have been replaced by milder and more environmentally friendly methods [6]. A variety of transition metal salts, such as $Yb(OTf)_3$ [7], $Bi(OTf)_3$ [8], $CeCl_3{\cdot}7H_2O$–NaI [9], and other Lewis acid catalysts [10], have also been applied in this reaction for the preparation of 3-substituted indoles, which are important substructures and building blocks for the synthesis of natural products and therapeutic agents [11]. However, several of those procedures still suffer some drawbacks, e.g., the need of strong acidic conditions, the use of stoichiometric amounts of Lewis acids and toxic expensive heavy metals. Hence, new efficient, selective and green procedures are still in strong demand, the searching of cheaper, simpler, and more efficient procedures (simple chemistry), including metal-free organocatalysts, is very attractive.

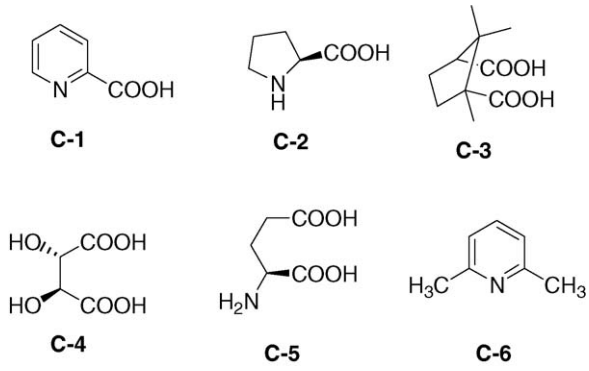
It is well known that 2,6-pyridinedicarboxylic acid is a relatively stable, easy to handle solid that is insensitive to small amounts of air and moisture. However, to the best of our knowledge, there are no any reports about the application in catalysis as a brønsted acidic organocatalyst. Herein, we report the first example of the PDA-catalyzed Michael-type Friedel-Crafts reactions of indoles with α,β-unsaturated enones and the acetalization of aldehydes.

We initially explored the reaction of chalcone **1a** and indole in the presence of 10 mol% PDA in CH_2Cl_2 at room temperature (Scheme 1). But no adduct was obtained, it may be due to the poor solubility of PDA in above solvent. Then we researched the reaction in different solvents, and found that the reaction proceeded smoothly in the presence of PDA (10 mol%) and anhydrous MeOH (3 ml) at room temperature giving the target product **3a** in good yield (80%), while no reaction occurred in other non-alcohol solvents, such as ether, CH_3CN, toluene, DMF, and water. The data listed in Table 1 (entries 1–3) indicated that alcohol was crucial for the PDA-catalyzed Michael-type Friedel-Crafts reaction of indole.

We continued our studies by screening a number of known and novel organocatalysts (Scheme 2: **C1**–**C6**) for the Michael-



Scheme 1.



Scheme 2.

type Friedel-Crafts reaction of indole with chalcone **1a**. Interestingly, it was observed that all these organic acids (**C1**–**C5**) and the combination of base (**C6**) with these acids were not effective and only trace products were formed even in anhydrous CH_3OH for one week. Moreover, no product was obtained when these organic brønsted acid were employed in other solvents, which implied that the PDA had special catalytic activity in this reaction.

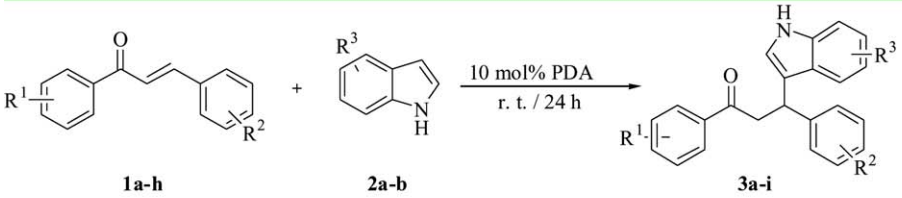
Encouraged by this result, we extended the scope to a variety of different indoles and enones. As shown in Table 1 (entries 3–11), all examples reacted smoothly at room temperature for 24 h, and the isolated yields were good in almost all cases (63–85%). It is interesting to compare several entries from Table 1. The yields were not sensitive to the substrates employed. Nearly all reactions are similarly in isolated yields, and the reaction is clean with no formation of side products like dimers or trimers, which are normally observed by the influence of strong acids.

As for the mechanism, we presumed that the reaction might proceed through the acidic hydrogen bonds based catalysis [12], or named classic proton catalysis (brønsted acid) [13]. The solvent-coordinated brønsted acid would activate carbonyl ketone and orientation leading to the occurring of subsequent reaction. Similarly to double hydrogen-bonding urea, which only suitable to activate the nitro group [14], PDA was not effective for the reaction of indole with α,β-unsaturated ester, which probably confirmed by the reason that brønsted acidic PDA would activate the carbonyl group acceptor of enone by double hydrogen-bonding motif (Scheme 3) [15].

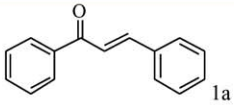
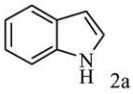
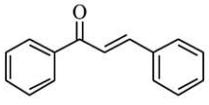
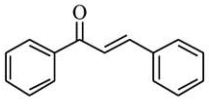
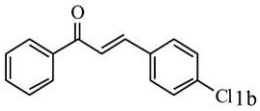
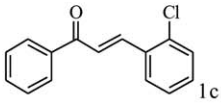
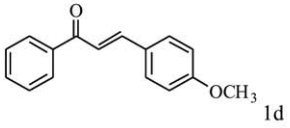
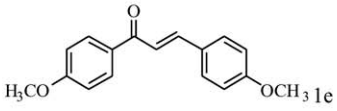
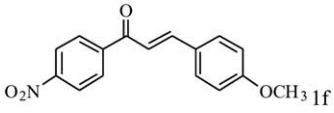
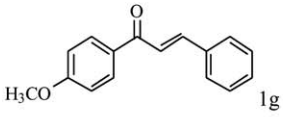
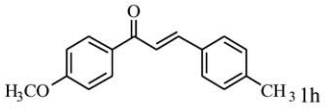
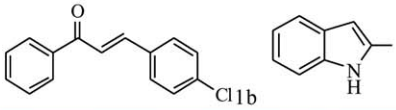
In assessing the versatile catalytic activity of PDA, we were pleased to find the acetalization of aldehydes with alcohol to give the corresponding acetals in excellent yields.

Acetal functions are recognized as good protecting groups of carbonyl functions and are widely used in synthetic organic chemistry [16]. So conversion of carbonyl compounds to the corresponding acetals is an important synthetic transformation that has received much attention. Generally, the conversion is performed in the presence of inorganic acids at reflux temperature for a long time, but the products are tolerant to neutral and basic conditions [17]. Recently, DDQ [18], $Bi(OTf)_3$ [19], $TiCl_4/Et_3N$ [20], and $RuCl_3$ [21] were used as efficient catalysts in this transformation. Nevertheless, there are still some draw-

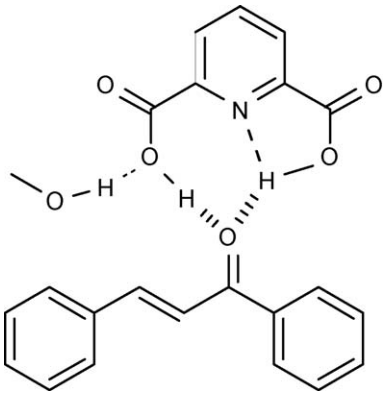
Table 1
PDA-catalyzed Michael-type Friedel-Crafts reactions of indoles with α,β-unsaturated enones[a]



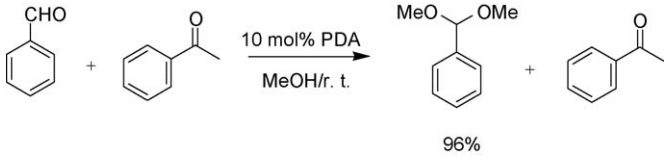
1a-h **2a-b** **3a-i**

Entry	Enone	Indole	Solvent	Yield[b] (%)
1	 1a	 2a	CH_2Cl_2	**3a**: N.R.
2	 1a	2a	EtOAc	**3a**: N.R.
3	 1a	2a	MeOH	**3a**: 80
4	 1b	2a	MeOH	**3b**: 78
5	 1c	2a	MeOH	**3c**: 70
6	 1d	2a	MeOH	**3d**: 64
7	 1e	2a	MeOH	**3e**: 63
8	 1f	2a	MeOH	**3f**: 68
9	 1g	2a	MeOH	**3g**: 74
10	 1h	2a	MeOH	**3h**: 70
11	 1b	2b	MeOH	**3i**: 85

[a] General reaction conditions: enone (1 mmol), PDA (0.1 mmol), indole (1.1 mmol), solvent (3 ml), 24 h, at room temperature.
[b] Isolated yields.



Scheme 3.

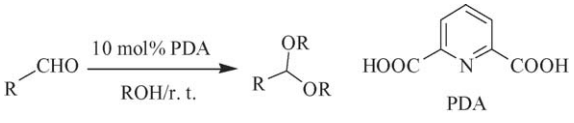


Scheme 4.

backs, e.g., $TiCl_4$, HCl, DDQ, and $BF_3{\cdot}Et_2O$ are rather corrosive and toxic. Therefore, it is a great need to develop a simple and efficient method for chemoselective protection of aldehydes in the presence of ketones [22]. The following paragraph is about our research on a mild and general procedure for the chemoselective conversion of aldehydes to the corresponding acetals in good yields using PDA as catalyst (Scheme 4).

The starting point of our research was to identify the optimal reaction condition in the acetalization of carbonyl compounds. Excitingly, the reaction of benzaldehyde with methanol in the presence of 10 mol% PDA at room temperature gained the desired acetal in excellent yield (96%). Similarly, benzaldehyde treated with ethanol in the presence of 10 mol% PDA produced the corresponding acetal in 93% yield. Also wide variety of aldehydes underwent smooth reactions giving the corresponding acetals in good yields. As shown in Table 2, several activated and deactivated aromatic aldehydes and aliphatic aldehydes were employed in the protection reactions to afford the corresponding acetals without exception. It is notable that the method provides a highly chemoselective acetalization of an aldehyde in the presence of a ketone. For instance, when an equimolar mixture of benzaldehyde and acetophenone was reacted with methanol in the presence of a catalytic amount of PDA, only the acetal of benzaldehyde was obtained, while the ketone was completely recovered (Scheme 4). In a word, this new method has the great advantages of high chemoselectivity, good to excellent yields, no need Dean-Stark trap and milder conditions, which make it a useful and important complementary to the present methodologies and suitable for practical small- and large-scale reactions.

Table 2
PDA-catalyzed protection of aldehydes as acetals[a]



Entry	Aldehyde	Alcohol	Yield[b] (%)
1	Benzaldehyde	MeOH	96
2	Benzaldehyde	EtOH	93
3	*p*-Tolualdehyde	MeOH	99
4	2-Chlorobenzaldehyde	MeOH	84
5	2,6-Dichlorobenzaldehyde	MeOH	99
6	Cinnamaldehyde	MeOH	60
7	2,6-Dichlorobenzaldehyde	*i*-PrOH	50 (91)[c]
8	4-Chlorobenzaldehyde	MeOH	99
9	Hydrocinnamaaldehyde	MeOH	99
10	4-Chlorobenzaldehyde	EtOH	92

[a] General reaction conditions: aldehyde (2 mmol), PDA (0.2 mmol), MeOH, 24 h at room temperature.
[b] Yields determined by GC.
[c] The number in parenthesis is the total yield of acetal and hemiacetals.

4. Conclusions

In summary, we have developed the first example of 2, 6-pyridinedicarboxylic acid used as organic catalyst in different reactions. This brønsted acidic organocatalyst could be employed in the chemoselective acetalization of aldehydes as acetals, and in the metal-free Michael-type Friedel-Crafts reactions of indoles with α,β-unsaturated enones. The procedure reported here has the advantages of mild reaction conditions, high yields of products, cleaner reactions with greater selectivity, operational simplicity, and simple work-up procedures makes it a useful and attractive process for the synthesis of alkylated indole derivatives and acetals.

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