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SHORT COMMUNICATION

Chiral Phosphoric Acid Catalyzed Enantioselective Aza-Michael Addition of Aromatic Amines to Nitroolefins

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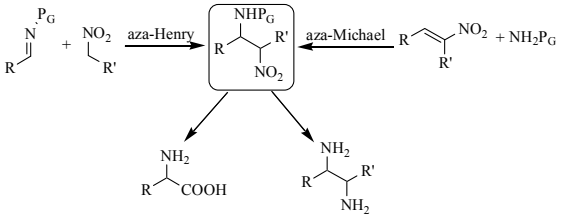
Abstract: Chiral phosphoric acid was found to be an effective organocatalyst in the enantioselective aza-Michael addition of aromatic amines to nitroolefins giving the corresponding β-nitroamine products in good yields (65%–95%) with moderate to good enantiomeric excess (16%–70%). This study represents the first example of a chiral phosphoric acid catalyzed asymmetric aza-Michael addition reaction.

Key words: chiral phosphoric acid; aromatic amine; nitroolefin; aza-Michael addition

β-nitroamines are ubiquitous structural motifs found in biologically important natural products and pharmaceutically active compounds, and they are also useful synthetic building blocks in organic synthesis especially for the synthesis of nitrogen-containing compounds [1]. Using well-established transformation chemistry, the β-nitroamines can be easily converted into α-amino acids or other α-aminocarbonyl compounds and vicinal diamines through the Nef reaction by the reduction of the nitro group [2]. Therefore, the development of an efficient synthetic method leading to β-nitroamines and their derivatives has attracted much attention in organic synthesis. Among the traditional methods used to generate β-nitroamines, the nucleophilic addition of nitroalkanes to imines and related compounds (aza-Henry or nitro-Mannich reaction) [3,4] is a powerful synthetic methodology that allows for the creation of two vicinal stereogenic centers bearing nitro and amino functional groups. Alternatively, because of its simplicity and atom economy the 1,4-addition of nitrogen nucleophiles to nitroolefins (aza-Michael reaction) is a convenient way to introduce this amine-based functionality to β-carbons that are attached to nitro groups (Scheme 1) [5–16]. Nevertheless, compared with the former method for generating β-nitroamines, only a few reports of the corresponding aza-Michael addition of nitrogen reagents to nitroolefins have been documented in the literature wherein their asymmetric construction was achieved mainly through the use of chiral substrates [17]. For example, Mioskowski and co-workers recently described the first diastereoselective synthesis of 1,2-diamino-3,3,3-trifluoropropane using readily available optically pure 4-phenyl-2-oxazolidinone as a nitrogen nucleophile [18–20]. In contrast, only one very recent example exists of the asymmetric catalytic aza-Michael addition of aromatic amines to nitroolefins. Ooi and co-workers reported the first highly enantioselective conjugate addition of 2,4-dimethoxyaniline to nitroolefins using chiral aminophosphonium cations as catalysts [21]. Obviously, the development of the catalytic asymmetric aza-Michael addition for the synthesis of chiral β-nitroamines remains challenging and elusive.

Over the last few years, novel chiral Brönsted acids have emerged as versatile enantioselective catalysts and their use in a variety of enantioselective transformations has been widely reported [22–26]. In this context, chiral phosphoric acids have been shown to be excellent chiral organocatalysts for the



Scheme 1. Synthesis and transformation of β-nitroamines.

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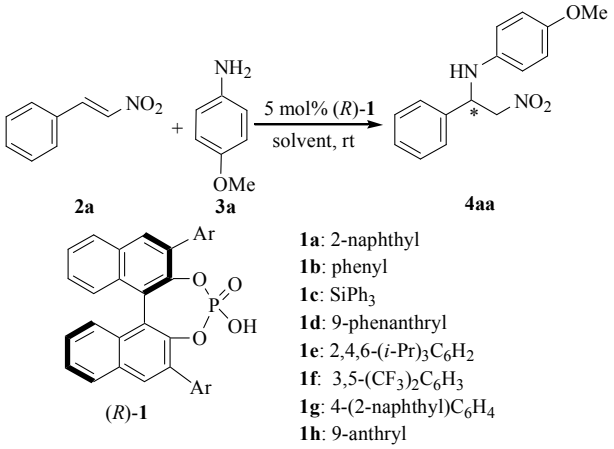
asymmetric activation of various substrates through hydrogen bonding interactions and these include imines, enamides, nitroolefins as well as ketones [27–30]. Recently, we have demonstrated that a cooperative catalytic system, produced by the combination of an iron salt and a chiral phosphoric acid, is able to catalyze the enantioselective Friedel-Crafts alkylation of indoles with β-aryl α′-hydroxy enones [31]. Inspired by our successful employment of chiral phosphoric acid catalysts [32] and following our long-standing interest in aza-Michael reactions [33–37], we envisioned that the synthesis of chiral β-nitroamines might be achievable by exploring the chiral phosphoric acid catalyzed aza-Michael addition reaction of aromatic amines to nitroolefins. Herein, we would like to report our preliminary results on the chiral phosphoric acid catalyzed enantioselective aza-Michael addition of aromatic amines to nitroolefins.

The general procedure for the catalytic asymmetric aza-Michael addition was as follows. To a flame-dried reaction tube was added 2-nitrovinylbenzene (**2a**, 0.2 mmol), chiral phosphoric acid (**1a**, 5 mol%), and a solvent (1 ml) at room temperature and under Ar. After 20 min of stirring at the same temperature the reactor was cooled to –20 °C and the aromatic amine (**3a**, 0.3 mmol) was also added at the same temperature. After the reaction was complete the crude product was purified directly by flash chromatography using ethyl acetate/petroleum ether (1:10) to afford the desired pure addition product. The enantiomeric excess (ee) was determined by chiral HPLC on Chiralpak IA, AS-H or OD-H columns. The spectral data of some representative products are given below. **4aa**: yellow oil. (Chiral HPLC was performed on a HP series 1200 and Chiralpak AS-H column. hexane/2-propanol = 9, 1.0 ml/min, 210 nm) t_{minor}: 47.56 min, t_{major}: 39.33 min, 26% ee; $[\alpha]_D^{20}$= –3.4 (*c* 0.21, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.29 (m, 5H), 6.66–6.64 (m, 2H), 6.52–6.49 (m, 2H), 5.00 (m, 1H), 4.61 (d, 2H, *J* = 6.4 Hz), 4.09 (s, 1H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 138.6, 137.0, 128.2, 127.6, 125.5, 113.9, 113.8, 79.1, 56.7, 54.6. **4af**: yellow oil. (Chiral HPLC was performed on a HP series 1200 and Chiralpak IA column. hexane/2-propanol = 9, 1.0 ml/min, 210 nm) t_{minor}: 15.33 min, t_{major}: 16.74 min, 54% ee; $[\alpha]_D^{20}$= –9.2 (*c* 0.54, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 7.23–7.18 (m, 2H), 6.49–6.45 (m, 2H), 5.14–5.09 (m, 1H), 4.73–4.64 (m, 2H), 4.48 (d, 1H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 137.2, 132.1, 129.4, 128.9, 126.4, 115.6, 110.8, 80.0, 56.7. **4ah**: yellow viscous oil. (Chiral HPLC was performed on a HP series 1200 and Chiralpak AS-H column. hexane/2-propanol = 9, 1.0 ml/min, 210 nm) t_{minor}: 22.70 min, t_{major}: 25.25 min, 16% ee; $[\alpha]_D^{20}$= –3.6 (*c* 0.11, CH_2Cl_2). The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the reported value[21]: $[\alpha]_D^{29}$= 10.8 (*c* 1.77, $CHCl_3$), 95% ee for (*S*)-isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 5H), 6.44–6.42 (m, 2H), 6.29 (1H, dd, *J* = 8.8, 2.4 Hz), 5.11 (s, 1H), 4.76–4.66 (m, 2H), 3.82 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 148.4, 138.2, 129.7, 129.2, 128.5, 126.5, 112.0, 103.7, 99.3, 80.2, 57.4, 55.7, 55.6.

Our initial focus was on the optimization of the reaction conditions (Table 1). Using toluene as the solvent and 4-methoxyaniline as the nitrogen nucleophile, a series of chiral phosphoric acids with different substituents at the 3,3′-positions of the binaphthyl scaffold were prepared and screened to find the best catalyst (entries 1–9). The results revealed that the chiral phosphoric acid **1a** was superior in terms of the observed selectivity of the aza-Michael addition product of nitrostyrene and 4-methoxyaniline (entry 1). The solvent also had a major effect on both the enantioselectivity and reactivity of the product. The use of nonpolar and weakly polar solvents gave promising results in terms of the product yield (entries 10–12). The more polar solvent resulted in a lower ee and a lower yield of the addition product compared with the weakly polar solvents (entry 13). From the solvent study, we determined that tetrahydrofuran (THF) was the best choice (entry 10). Decreasing the reaction temperature to –20

Table 1 Optimization of the aza-Michael addition



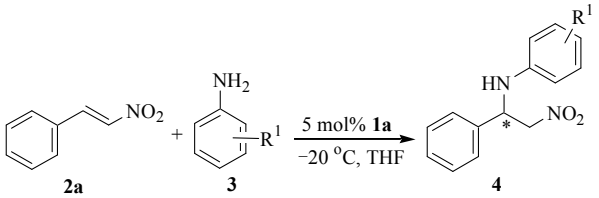
Entry	Catalyst	Solvent	Time (h)	Yield (%)	ee/%
1	**1a**	toluene	24	80	14
2	**1b**	toluene	24	95	9
3	**1c**	toluene	24	70	0
4	**1d**	toluene	24	85	7
5	**1e**	toluene	24	85	10
6	**1f**	toluene	24	92	8
7	**1g**	toluene	24	87	4
8	**1h**	toluene	24	90	0
9	**1i**	toluene	24	90	9
10	**1a**	THF	24	85	20
11	**1a**	$CHCl_3$	24	80	8
12	**1a**	xylene	24	95	11
13	**1a**	1,4-dioxane	24	60	0
14[a]	**1a**	THF	48	86	23
15[a,b]	**1a**	THF	48	89	26

Reaction conditions: 5 mol% **1**, 0.2 mmol **2a**, 0.3 mmol **3a**, 1 ml solvent, under Ar.

[a]The reaction was run at –20 °C.

[b]0.3 nm molecular sieves (100 mg) were added.

Table 2 Chiral phosphoric acid **1a** catalyzed asymmetric aza-Michael addition of aromatic amines to 2-nitrovinylbenzene



Entry	R^1 in **3**	Time (h)	**4**	Yield (%)	ee/%
1	H **3b**	36	**4ab**	80	40
2	4-Me **3c**	36	**4ac**	85	30
3	4-CF_3 **3d**	48	**4ad**	—	—
4	4-Cl **3e**	48	**4ae**	65	43
5	4-Br **3f**	48	**4af**	70	54
6	4-F **3g**	48	**4ag**	80	43
7	2,4-$(OMe)_2$ **3h**	36	**4ah**	76	16

Reaction conditions: 5 mol% **1a**, 0.2 mmol **2a**, 0.3 mmol **3**, 1 ml THF, 0.3 nm molecular sieves (100 mg), at –20 °C, in Ar.

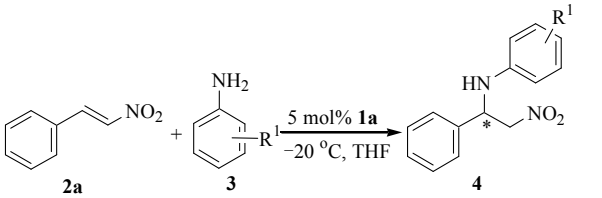
[a]The absolute configuration of **4ah** was assigned as (*R*) by comparison of the optical rotation with the reported value [21].

°C resulted in increased ee of the addition product (entry 14). Further optimization of the reaction conditions revealed that the addition of 0.3 nm molecular sieves could improve the ee of the addition product (entry 15).

With the optimized reaction conditions in hand, we turned our attention to the effect of substituent groups on the various aromatic amines (Table 2). A variety of amines were investigated for the generality of this reaction under the optimized reaction conditions. As shown in Table 2, amine **3b**, which had no substituent on the phenyl ring (entry 1) and the amines containing electron-withdrawing groups on the phenyl ring (entries 4–6) were good substrates. They provided the addition products in good yields with high ee values. In contrast, a slight decrease in ee was observed for the amine bearing electron-donating group on the phenyl ring (entry 2). Along with the electronic effect, the steric effect was also obvious in this reaction (entry 7). It should be noted that when the phenyl ring of the aromatic amines had more electron-withdrawing groups such as CF_3 the aza-Michael reaction did not occur at all (entry 3).

Further exploration of this novel chiral phosphoric acid catalyzed asymmetric aza-Michael addition of 4-bromoaniline **3f** was conducted using various substituted nitroolefins. As listed in Table 3, the halogenated nitroolefins gave the corresponding products in good yields with moderate ee values (entries 1–2). An increase in ee values was observed when the steric hindrance of the aromatic ring in the nitroolefin was increased (entry 5). To our delight moderate to good product yields and ee values were obtained when election-donating groups such as OMe were present on the phenyl ring of the nitroolefins (entries 3 and 6). It was surprising that no product was observed when 4-methoxynitrostyrene **2e** was employed (entry 4). Finally, various substituted aromatic amines were

Table 3 Scope of the enantioselective aza-Michael addition catalyzed by chiral phosphoric acid 1a



Entry	R in **2**	Ar in **3**	**4**	Yield (%)	ee/%
1	4-Br **2b**	4-BrC_6H_4 **3f**	**4bf**	82	19
2	4-Cl **2c**	4-BrC_6H_4 **3f**	**4cf**	81	30
3	2-OMe **2d**	4-BrC_6H_4 **3f**	**4df**	65	44
4	4-OMe **2e**	4-BrC_6H_4 **3f**	**4ef**	—	—
5	2-Br **2f**	4-BrC_6H_4 **3f**	**4ff**	85	45
6	2,3-$(OMe)_2$ **2g**	4-BrC_6H_4 **3f**	**4gf**	85	70
7	4-Me **2h**	Ph **3b**	**4hb**	70	30
8	4-Me **2h**	4-MeC_6H_4 **3c**	**4hc**	75	30
9	4-Me **2h**	4-FC_6H_4 **3g**	**4hg**	70	42
10	4-Me **2h**	2-Naphthyl **3i**	**4hi**	64	48

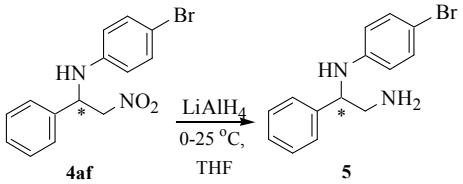
Reaction conditions: 5 mol% **1a**, 0.2 mmol **2**, 0.3 mmol **3**, 1 ml THF, 0.3 nm molecular sieves (100 mg), –20 °C, 48 h, in Ar.

[a]At –20 °C for 36 h.

also investigated in the aza-Michael addition reaction with 4-methylnitrostyrene **2h** as the substrate. The electronic and steric effects of the aromatic amines were all important for the enantioselectivities of the addition products (entries 7–10). Although the exact mechanism of this addition reaction is not clear at current stage, on the basis of the results that we obtained here and previously [32], a plausible transition state model which involves the acidic proton of phosphoric acid for activation the nitro moiety and the phosphoryl oxygen atom activation the aromatic amine N–H moiety through the hydrogen bond is the most likely involved.

To demonstrate the synthetic use of the current methodology for the synthesis of vicinal diamine derivatives, the reduction of the nitroamine derivative was evaluated. As shown in Scheme 2, after a work-up of the reaction of nitroamine **4af** (54% ee) with $LiAlH_4$, the desired diamine derivative **5** was obtained in 74% yield with 34% ee, which indicated a slight racemization during the reduction process.

In conclusion, we developed an efficient method for the enantioselective aza-Michael addition reaction between aromatic amines and nitroolefins using chiral phosphoric acids as catalyst for the first time. The aza-Michael addition products were generally obtained in good yields (65%–95%) with moderate to good enantiomeric excesses (16%–70%). Further



Scheme 2. Reduction of the β-nitroamine product.

studies into improving the selectivity and the scope of this reaction and related aza-Michael reactions catalyzed by chiral Brönsted acids are ongoing in our lab and will be reported in due course.

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