Published in final edited form as:

Tetrahedron Lett. 2013 October 16; 54(42): . doi:10.1016/j.tetlet.2013.08.015.

Organocatalyzed asymmetric Michael reaction of β -aryl- α -ketophosphonates and nitroalkenes

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Abstract

The first enantioselective Michael reaction of β -aryl- α -ketophosphonates and nitroalkenes has been realized by using a new bifunctional Takemoto-type thiourea catalyst. The primary Michael adducts obtained were converted in situ to the corresponding amides through the aminolysis. High yields, excellent diastereoselectivities (>95:5 dr), and good enantioselectivities (up to 81% ee) have been achieved for the corresponding β -disubstituted α -nitroamides. This reaction again demonstrated that β -ketophosphonates are interesting pronucleophiles that can be used as amide surrogates in organocatalyzed reactions.

Keywords

Michael reaction; Organocatalysis; β -Ketophosphonate; Nitroalkene; Enantioselective; Amide surrogate

The Michael reaction is one of the most important tools for the carbon-carbon formation in organic chemistry and, therefore, it has found extensive applications in the asymmetric synthesis of chiral compounds.¹ In the past decade, organocatalyzed Michael reactions have been widely studied as one of most economical and environmentally friendly strategies in asymmetric catalyses.² Among the various Michael acceptors, nitroalkenes attract particular attentions owing to their high electrophilicity and the various functional group transformations available for the nitro group.³ Besides the enamine-mediated catalysis involving the more electrophilic ketones and aldehydes as the pronucleophiles in the organocatalyzed Michael reactions,⁴ a large number of reactive Michael donors, such as 1,3-dicarbonyl compounds,⁵ 1,2-dicarbonyl compounds,⁶ phosphites,⁷ and oxindoles⁸ have been applied in the reactions with nitroalkenes using organic Brønsted base catalysts. However, the direct use of an ester or an amide as the substrate in both mechanisms remains very challenging due to their poor electrophilic carbonyl groups (precluding the direct formation of an enamine intermediate using an amine catalyst) and their high pK_a values (precluding the direct formation of an enolate intermediate using organic Brønsted bases). To circumvent this problem, Wennemers and coworkers chose malonic acid half thioesters and

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Supplementary Data

Detailed experimental procedures and copies of ¹H, ¹³C NMR spectra and HPLC chromatograms. Supplementary data associated with this article can be found in the online version, at

mono thiomalonate as the surrogates of esters/amides.⁹ Nonetheless, with these substrates it is difficult to generate a substituent at the α -position of the ester/amide group in the Michael products. Most recently, Barbas and coworkers used a pyrazoleamide as an ester surrogate and accomplished an organocatalyzed Michael reaction using a special amide as the donor.¹⁰ Despite the fact that excellent results were normally achieved, the electronic nature of the substituent on the pyrazoleamide aromatic ring has a major influence on the reactivity of this reaction. Whenever there is an electron-donating group, the yield of the reaction is merely modest. Thus, the development of new ester/amide surrogates that can be applied in organocatalyzed Michael reactions with nitroalkenes is not only warranted but highly desirable. It should be also pointed out that the products of this Michael reaction (α -nitroesters or α -nitroamides) is very important: They are analogues of γ -aminobutyric acid (GABA).¹¹ GABA is the chief inhibitory neurotransmitter in the mammalian central nervous system.¹²

It is known that α -ketophosphonate group can be easily converted into an ester or amide group.¹³ Previously, Jørgensen and coworkers also used α , β -unsaturated α -ketophosphonates as surrogates of α , β -unsaturated esters/amides in an organocatalyzed Michael reaction.¹⁴ Most recently, we successfully realized the first direct application of acetylphosphonate as an enolate precursor¹⁵ in Brønsted base-catalyzed aldol reactions.¹⁶ The products obtained in the aldol reactions were efficiently converted in situ into the corresponding esters or amides. Thus, we demonstrated that α -ketophosphonate is an excellent surrogate for ester/amide that can be applied in organic Brønsted base-catalyzed enolate-mediated reactions. To further demonstrate the usefulness of these compounds as surrogates of esters/amides in organocatalytic reactions, herein we wish to disclose the first organocatalyzed asymmetric Michael reaction of α -aryl- α -ketophosphonates¹⁷ with nitroalkenes using chiral bifunctional Brønsted base catalysts. Once the Michael addition reactions was finished, the α -ketophosphonate group was in situ converted to an amide group through aminolysis to give the corresponding α , β -disubstituted α -nitroamides in high yields and good stereoselectivities.

On the basis of our previous findings in the Brønsted base-catalyzed asymmetric aldol reaction of acetylphosphonates,¹⁵ we chose dimethyl 2-phenylacetylphosphonate (**1a**) and *trans*- α -nitrostyrene (**2a**) as the model substrates to screen several readily available bifunctional Brønsted base catalysts (Figure 1) for the desired Michael reaction. Once the reaction was completed, the aminolysis of the α -ketophosphonate group was achieved with methanamine in a one-pot fashion to give the corresponding α , β -diphenyl- α -nitroamide product **3a**. The results of the screening are summarized in Table 1. As the data in Table 1 show, when 9-*O*-(1-naphthylmethyl)cupreidine (**4a**) was used as the catalyst in THF at rt for 4 h, the desired product **3a** was obtained in 61% yield with a dr of 80:20. The major *anti*-diastereomer was obtained in a low ee value of only 11% (Table 1, entry 1). In contrast, when the quinidine-derived thiourea **4b** was used under similar conditions, product **3a** was obtained in a high yield of 90%. The dr of the product was 85:15 and the opposite enantiomer [(2*S*,3*R*)] of the major *anti*-diastereomer was obtained in 51% ee (entry 2). Similarly, when the Takemoto-type thiourea catalyst^{5a} **4c** was used, the dr value of the reaction was slightly improved to 90:10 while the enantioselectivity of this reaction remained at 50 % ee (entry 3). Encouraged by these results, we further screened some additional bifunctional catalysts with the *trans*-cyclohexanediamine scaffold. When the thiourea group in catalyst **4c** is replaced by a squareamide, as in catalyst **4d**, there was no change in the dr of this reaction; however, the ee value obtained for **3a** dropped to 40% (entry 4). Similarly, modification on the aryl group of the thiourea moiety (to a phenyl group, catalyst **4e**) or modification on both the aryl group and the tertiary amine group (catalyst **4f**) proved to be unhelpful for improving the dr or the enantioselectivity of this reaction (entries 5 and 6). To further improve the enantioselectivity of this reaction, the

steric factors of the thiourea moiety were finely tuned. Thus, we designed and synthesized two new catalysts **4g** and **4h**, which contain a more bulky 2,6-diisopropylphenyl group on the thiourea moiety. To our pleasure, a slightly higher ee value of 64% was obtained for **3a** when catalyst **4g** was applied, without compromising the yield and the dr value (entry 7). When **4h** was employed as the catalyst, an ee value of 57% was obtained (entry 8). Thus, catalyst **4g** was identified as the best catalyst for this reaction. Next, the solvent used in the reaction was optimized. It was found that solvent did not have any major influence on the reaction in terms of the product yield or ee value (entries 8-12); however, slightly higher dr values were obtained in methylene chloride (entry 10), toluene (entry 11), and benzene (entry 12). Methylene chloride was selected as solvent of choice since a slightly better yield was also obtained in this solvent (entry 10). Lowering the reaction temperature to $-10\text{ }^{\circ}\text{C}$ led to a higher yield for **3a** (95%, entry 13). Under these conditions, product **3a** was obtained as a single diastereomer (dr > 95:5) with an ee value of 78% (entry 13).

Once the reaction conditions were optimized, the scope of this reaction was then established, and the results are summarized in Table 2. As is evident from the data in Table 2, *trans*-nitrostyrene derivatives with either an electron-donating or an electron-withdrawing group on the phenyl ring all gave the desired formal amide Michael adducts with excellent yields and diastereoselectivities (Table 2, entries 1-6). Slightly higher ee values were obtained for *trans*-nitrostyrenes with an electron-donating group (entries 2 and 3), which also reacted slightly slower. *trans*-(1-Naphthyl)nitroethene (entry 7) also yielded the desired Michael adduct **3g** in a high yield and excellent dr, albeit with a slightly lower ee value of 67%. A high yield and good dr could also be obtained for a *trans*-alkyl-substituted nitroethene (entry 7), which yielded one of the highest ee values for the corresponding Michael product **3h** (81% ee, entry 8). We also explored the scope of the *trans*-aryl-ketophosphonates using *trans*-nitrostyrene as the Michael acceptor (entries 9-12). Apparently, the electronic nature of substituent on the phenyl ring has little influence on the reactivity, diastereoselectivity, or the enantioselectivity of this reaction since similar results were obtained for compounds with an electron-donating group or an electron-withdrawing group at the *para*-position of the phenyl ring (entries 9-12).

The absolute configuration of the major enantiomer obtained in this reaction was determined through the X-ray crystallographic analysis using compound **3d**.¹⁸ As shown in Figure 2, compound **3d** has an absolute configuration of (2*R*,3*S*). The stereochemistry of the other products was similarly assigned on the basis of the reaction mechanism.

On the basis of the stereochemistry of the major stereoisomer formed in this reaction, a plausible mechanism of this reaction was proposed. As shown as in Scheme 1, the tertiary amine moiety of catalyst **4g** first deprotonates the *trans*-aryl-ketophosphonate. After deprotonation, the enolate associates closely with the catalyst through ionic interactions and potentially also hydrogen bonding between the ammonium and enolate. Simultaneously, the nitroalkene is hydrogen-bonded to the thiourea moiety of the catalyst. These hydrogen bonds not only help fix the orientation of the nitroalkene but also activate the electrophile. Due to the unfavorable interactions between the large phosphoryl group and the catalyst as well as those between the two aryl groups of the substrates (Scheme 1, lower equation), the attack of the enolate using its *Si* face to the *Re* face of the nitroalkene is disfavored. Instead, the attack of the *Si*-face of the nitroalkene using the enolate *Re* face is favored (Scheme 1, upper equation), which leads to the observed major (2*R*,3*S*)-diastereomer after aminolysis.

In summary, we have realized the first enantioselective Michael reaction of *trans*-aryl-ketophosphonates and nitroalkenes by using a new Takemoto-type catalyst and demonstrated that *trans*-aryl-ketophosphonate may be used as an amide surrogate in organocatalyzed Michael reactions. The corresponding formal amide Michael adducts were

obtained in excellent yields and diastereoselectivities with good enantioselectivities (up to 81% ee).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The generous financial support of this project from the Welch Foundation (grant No. AX-1593) and the NIH-NIGMS (grant No. SC1-082718) is gratefully appreciated. The authors also thank Dr. Hadi Arman for help with the X-ray analysis of compound **3d**.

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Figure 1.
Catalysts screened in the Michael reaction.

Figure 2.
ORTEP drawing of compound **3d**.

Scheme 1.

Proposed transition states of the Michael reaction of *trans*- β -nitrostyrene and α -aryl- β -ketophosphonate.

Table 1

Catalyst screening and optimization of the reaction conditions^a

Entry	Catalyst	Solvent	Yield (%) ^b	dr ^c	ee (%) ^d
1	4a	THF	61	80:20	11
2	4b	THF	90	85:15	51 ^e
3	4c	THF	85	90:10	50
4	4d	THF	80	90:10	40
5	4e	THF	83	90:10	49
6	4f	THF	88	90:10	45
7	4g	THF	90	90:10	64
8	4h	THF	80	90:10	57
9	4g	Et ₂ O	73	90:10	73
10	4g	CH ₂ Cl ₂	82	95:5	74
11	4g	Toluene	80	95:5	73
12	4g	Benzene	80	95:5	73
13 ^f	4g	CH ₂ Cl ₂	95	>95:5	78

^aUnless otherwise specified, all reactions were conducted with *trans*-nitrostyrene (**1a**, 0.10 mmol), dimethyl 2-phenylacetylphosphonate (**2a**, 0.20 mmol) and the catalyst (10 mmol %) in the specified solvent (0.5 mL) at rt.

^bCombined yield of both diastereomers after column chromatography.

^cDetermined by ¹H NMR analysis of the crude product.

^dDetermined by HPLC analysis using a ChiralPak IC column.

^eThe opposite (2*S*,3*R*)-enantiomer was obtained as the major product.

^fThe reaction was carried out at -10 °C.

Table 2

Substrate Scope of the Michael Reaction^a

Entry	R	Ar	3	Time (h)	Yield ^b (%)	dr ^c	ee ^d (%)
1	Ph	Ph	3a	4	95	>95:5	78
2	4-MeOC ₆ H ₄ -	Ph	3b	4	93	>95:5	81
3	4-MeC ₆ H ₄ -	Ph	3c	3	98	>95:5	78
4	4-BrC ₆ H ₄ -	Ph	3d	3	93	>95:5	78
5	4-ClC ₆ H ₄ -	Ph	3e	2	90	>95:5	73
6	3-BrC ₆ H ₄ -	Ph	3f	3	90	>95:5	74
7	1-Nap ^e	Ph	3g	2	92	>95:5	67
8	<i>n</i> -Pr	Ph	3h	4	84 ^f	90:10	81
9	Ph	4-MeOC ₆ H ₄ -	3i	3	95	>95:5	80
10	Ph	4-MeC ₆ H ₄ -	3j	2	93	>95:5	79
11	Ph	4-ClC ₆ H ₄ -	3k	4	95	>95:5	76
12	Ph	4-FC ₆ H ₄ -	3l	4	98	>95:5	78

^a All reactions were conducted with nitroalkene **1** (0.10 mmol), -aryl- -ketophosphonate **2** (0.20 mmol), and catalyst **4g** (0.010 mmol, 10.0 mmol %) in CH₂Cl₂ (0.5 mL) at -10 °C.

^b Yield of isolated product after column chromatography.

^c Determined by ¹H NMR analysis of the crude product.

^d Determined by HPLC analyses.

^e 1-Naphthyl.

^f Combined yield of both diastereomers.