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Highly Enantioselective Conjugate Additions of Phosphites to α,β-Unsaturated *N*-Acylpyrroles and Imines: A Practical Approach to Enantiomerically Enriched Amino Phosphonates

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Abstract: The first highly enantioselective phosphonylation of α,β-unsaturated *N*-acylpyrroles has been developed. Excellent yields (91–99%) and enantioselectivities (up to >99% enantiomeric excess (*ee*)) were observed for a broad spectrum of both phosphites and *N*-acylpyrroles under mild conditions. In particular, when diethyl phosphite was employed to test the scope of the *N*-acylpyrroles, almost optically pure products (98 to >99% *ee*) were obtained for 20 examples of *N*-acylpyrroles. Moreover, optically pure α-substituted β- or γ-amino phosphonates can be obtained by several simple transformations of the pyrrolyl phosphonates. The versatility of the *N*-acylpyrrole moiety makes the phosphorus adducts powerful chiral building blocks that enable the synthesis of various phosphonate-containing compounds. Finally, the present strategy can also be applied to the asymmetric hydrophosphonylation of *N*-acylimines with high enantioselectivities (93 to >99% *ee*).

Keywords: asymmetric catalysis · hydrophosphonylation · Michael addition · phosphonates · synthetic methods

Introduction

The catalytic asymmetric synthesis of optically active phosphonates provokes continuing interest because such compounds are usually precursors of many biologically active and pharmaceutically important molecules.[1] The direct addition of phosphite to electrophiles is, without a doubt, one of the most powerful methods to provide such compounds. Indeed, numerous studies have been focused on the asymmetric hydrophosphonylation of aldehydes,[2] imines,[2] and nitroalkenes[3] in recent decades. In contrast, the asymmetric conjugate additions of phosphites to α,β-unsaturated carbonyl compounds are still challenging and have been much less developed. To the best of our knowledge, there are only two catalytic examples presented to date.[4] In 2007, Jørgensen and co-workers[5] reported an organocatalytic enantioselective phosphonylation of α,β-unsaturated aldehydes. And recently, we[6] described the first enantioselective 1,4-addition of phosphite to α,β-unsaturated ketones by using a dinuclear zinc catalyst.[7] However, there is still high demand in both academia and industry for the asymmetric phospha-Michael reaction of α,β-unsaturated esters or their surrogates,[8] since these moieties can be readily converted to various functional groups. To achieve this goal, Quirion and co-workers[9] employed chiral amides and phosphonate salts to synthesize amidophosphonates (Scheme 1a). Unfortunately, the scope is limited and a catalytic version is still required. Herein, we report the first conjugate addition reactions of phosphites to α,β-unsaturated *N*-acylpyrroles catalyzed by a dinuclear zinc catalyst. Significantly, this new catalytic asymmetric phospha-Michael reaction afforded consistently ex-

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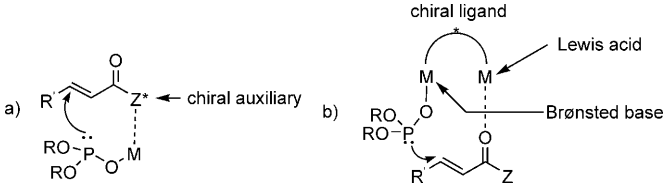


Scheme 1. a) Chiral auxiliary-induced asymmetric phospha-Michael reaction of α,β-unsaturated ester surrogates. b) Catalytic protocol for asymmetric hydrophosphonylation of α,β-unsaturated ester surrogates.

cellent enantioselectivities with a wide scope for both phosphites and *N*-acylpyrroles.

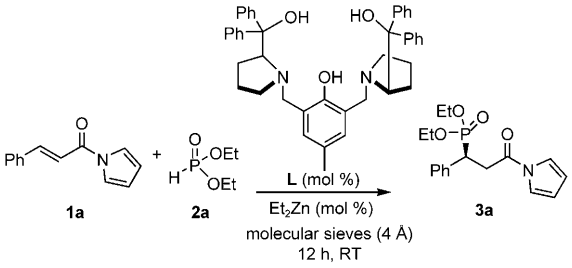
Results and Discussion

Recently, α,β-unsaturated *N*-acylpyrroles developed by Shibasaki and co-workers have proven to be highly reactive, monodentate ester surrogates.[10] Importantly, these compounds display similar reactivity to α,β-unsaturated ketones[10,11] and the *N*-acylpyrrole moiety of the adducts can be readily converted to the alcohol, aldehyde/ketone, or carboxylic acid derivatives.[12] On the other hand, we recently successfully carried out the phospha-Michael reaction of α,β-unsaturated ketones through a bifunctional mode of catalysis and we assumed that this strategy may also be applied to α,β-unsaturated *N*-acylpyrroles. That is, one metal of the catalyst functions as a Lewis acid to bind with the ester surrogate and another metal functions as a Brønsted base to activate the phosphite (Scheme 1b).

To test this assumption, the reaction of the *N*-acylpyrrole **1a** with diethyl phosphite (**2a**) in THF in the presence of 4 Å molecular sieves and 20 mol% catalyst was chosen as a model. We were pleased to find that *N*-acylpyrrole was stable enough in the catalytic system, such that the addition reaction proceeded in high yield and enantioselectivity (Table 1, entry 1). A solvent screen indicated that the reaction was able to tolerate a series of solvents. In particular, toluene gave the best yield and enantioselectivity (Table 1, entry 5). Thus, toluene was used for further optimization of the reaction conditions. When the catalyst loading was decreased to 10 mol%, the yield and enantioselectivity were both slightly affected.

Having established the optimal reaction conditions, we then examined a series of phosphites. As shown in Table 2, all dialkyl phosphites examined underwent the addition reaction in high yields and enantioselectivities (Table 2, entries 1–4). Among the phosphites tested, linear alkyl phosphites **2a** and **2c** gave the best yields and enantioselectivities (>99% *ee*). Interestingly, we found that diaryl phosphite **2e** was also amenable to the present catalysis system (Table 2, entry 5). By comparison, phosphites **2d** and **2e** with bulkier substituents were found to react more slowly and therefore longer reaction times were required.

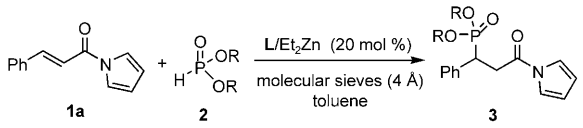
Table 1. Optimization of the phospha-Michael reaction of **1a** and **2a**.



Entry[a]	**L** [mol%]	Et_2Zn [mol%]	Solvent	Yield [%][b]	*ee* [%][c]
1	20	40	THF	84	98
2	20	40	Et_2O	94	99
3	20	40	hexane	89	98
4	20	40	CH_2Cl_2	84	99
5	20	40	toluene	99	>99
6	10	20	toluene	90	98

[a] All reactions were carried out with **1a** (0.25 mmol) and **2a** (0.375 mmol, 1.5 equiv) in solvent (2.5 mL) at room temperature for 12 h. [b] Yield of the isolated product. [c] The enantiomeric excess was determined by HPLC analysis on a Chiralpak AD-H column.

Table 2. Examination of the scope of phosphites.



Entry[a]	**2**	R	Product	Time [h]	Yield [%][b]	*ee* [%][c]
1	**2a**	Et	**3a**	12	99	>99
2	**2b**	Me	**3ba**	12	93	95
3	**2c**	*n*Pr	**3ca**	12	98	>99
4	**2d**	*i*Pr	**3da**	24	95	97
5	**2e**	Ph	**3ea**	24	96	92

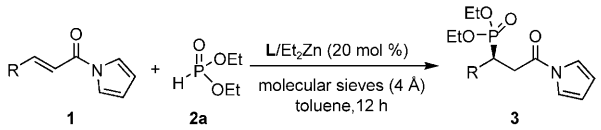
[a] Unless otherwise noted, reactions were carried out with **1a** (0.25 mmol) and **2** (1.5 equiv) in toluene (2.5 mL) at room temperature. [b] Yield of the isolated product. [c] The enantiomeric excess was determined by HPLC analysis (see the Supporting Information).

The scope of the α,β-unsaturated *N*-acylpyrroles was then investigated by using commercially available **2a**. As summarized in Table 3, the reaction was able to tolerate a broad range of substrates. For β-aryl-*N*-acylpyrroles, the adducts could be obtained in almost optically pure form, irrespective of the electronic nature or position of the substituents on the phenyl ring (Table 3, entries 1–6 and 10–14). Good results were also observed for various β-heteroaryl-*N*-acylpyrroles (Table 3, entries 7–9) and β-alkyl-*N*-acylpyrroles (Table 3, entries 16–20). Interestingly, the reaction proceeded stereoselectively and regioselectively with diene **1o** and despite the prolonged reaction time required, exclusive formation of the Michael adduct was observed (Table 3, entry 15). Importantly, when the phospha-Michael addition reaction was performed on a larger scale the yield and enantioselectivity were not significantly affected (Table 3, entry 21).

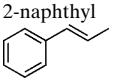
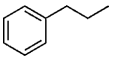
The synthetic utility of the phosphorous adducts was demonstrated by the following transformations (Scheme 2): The pyrrolyl phosphonates **3** can be easily transformed into methyl esters **4** in the presence of sodium methoxide in methanol. Reactions of pyrrolyl phosphonates **3a** with a primary or secondary amine gave the corresponding amides in good yields. Amide **6** can be further converted to γ-amino phosphonate **7** by reduction. It should be noted that phosphonate **3a** can be directly hydrolyzed by using NaOH to the corresponding carboxylic acid **8**, which can then be transformed into β-amino phosphonate[13] **9** by the well-established literature procedure.[14]

Interestingly, the present strategy can also be applied to the asymmetric hydrophosphonylation of imines. To date, several organocatalysts including chiral thiourea derivatives,[15] cinchona alkaloids,[16] and chiral phosphoric acids,[17]

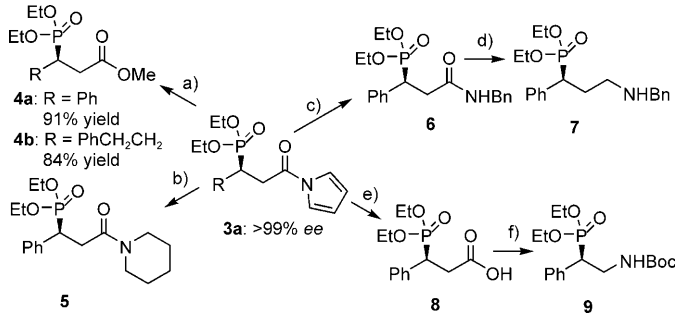
Table 3. Examination of the scope of α,β-unsaturated *N*-acylpyrroles.



1 2a 3

Entry[a]	1	R	Product	Yield [%][b]	*ee* [%][c]
1[d]	**1a**	Ph	**3a**	99	>99 (*S*)
2	**1b**	4-MeC_6H_4	**3b**	99	>99
3	**1c**	4-$MeOC_6H_4$	**3c**	99	>99
4	**1d**	4-ClC_6H_4	**3d**	96	>99
5	**1e**	4-BrC_6H_4	**3e**	98	>99
6	**1f**	4-FC_6H_4	**3f**	96	98
7	**1g**	2-furyl	**3g**	99	>99
8	**1h**	2-thienyl	**3h**	99	>99
9	**1i**	3-thienyl	**3i**	94	>99
10	**1j**	3-$MeOC_6H_4$	**3j**	94	99
11[e]	**1k**	2-$MeOC_6H_4$	**3k**	94	98
12	**1l**	4-$NO_2C_6H_4$	**3l**	96	98
13	**1m**	1-naphthyl	**3m**	95	98
14	**1n**	2-naphthyl	**3n**	97	>99
15[f]	**1o**		**3o**	91	>99
16	**1p**		**3p**	96	>99
17	**1q**	*n*Pr	**3q**	93	98
18	**1r**	*i*Pr	**3r**	99	99
19	**1s**	$CH_3(CH_2)_5$	**3s**	98	98
20	**1t**	$(CH_3)_2CHCH_2$	**3t**	92	>99
21[g]	**1a**	Ph	**3a**	98	>99

[a] Unless otherwise noted, reactions were carried out with **1** (0.25 mmol) and **2a** (0.375 mmol, 1.5 equiv) in 2.5 mL toluene at room temperature for 12 h. [b] Yield of the isolated product. [c] The enantiomeric excess was determined by HPLC analysis. [d] The absolute configuration of **3n** was determined as *S* by chemical correlation (see the Supporting Information) and the rest of the products were assigned by analogy. [e] Reaction time: 18 h. [f] Reaction time: 36 h. [g] Reaction performed on a 10 mmol scale.



Scheme 2. Synthetic utility of pyrrolyl phosphonates **3**. a) NaOMe, MeOH, 0°C, 10 min; b) piperidine, THF, reflux, 80%; c) NH_2Bn, THF, reflux, 91%; d) $BH_3{\cdot}SMe_2$, THF, 0°C–reflux, 79%; e) NaOH, MeOH, H_2O, RT, 2 h, 93%; f) $(PhO)_2PON_3$, Et_3N, toluene, *t*BuOH, reflux, 48 h, 48%. Bn = benzyl, Boc = *tert*-butoxycarbonyl.

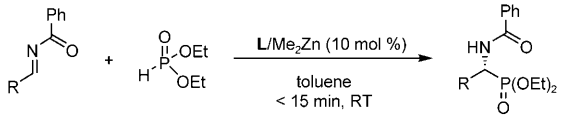
as well as metal catalysts, such as Shibasaki's heterobimetallic complexes,[18] chiral aluminium(III),[19] and chiral scandium(III)[20] have been successfully utilized for this reaction. However, there is still a great need for the development of a highly enantioselective and efficient catalytic system for this reaction.

In light of the similarity in structure between *N*-acylimines and chalcones, we speculated that the present method could be extended to the use of *N*-acylimines as substrates. Thus, *N*-acylimine **10a** was employed to examine the hypothesis under typical reaction conditions. It seems that the strategy was indeed effective for the hydrophosphonylation reaction (99% *ee*, 90% yield), however, the enantioselectivities were not reproducible. This problem was solved by using Me_2Zn instead of Et_2Zn to form the catalyst. In addition, it was found that 4 Å molecular sieves were not essential to achieve a good result for this reaction.

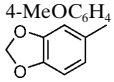
Under the modified reaction conditions (10 mol% of **L**/Me_2Zn in toluene at room temperature), the scope of the imines was then examined. We were pleased to find that the reaction showed particularly high reactivity for all imines investigated and reactions were complete within 15 min. Aromatic imines possessing substituents with differing electronic properties showed similar reactivity and enantioselectivity (Table 4, entries 1–9). Moreover, the condensed-ring imine **10j** and the aliphatic imine **10k** were also excellent substrates for the present system (Table 4, entries 10 and 11). It should be noted that this method provided the highest average enantioselectivities of the asymmetric hydrophosphonylation of imines to date.

Finally, the product **11a** can be readily converted into the corresponding amino phosphonic acid **12** (Scheme 3). The benzoyl and ester groups were removed by treating **11a**

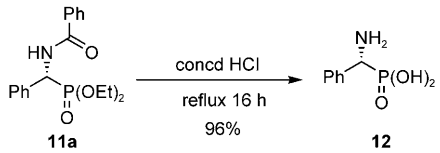
Table 4. Examination of the scope of imines.



10 2a 11

Entry[a]	10	R	Product	Yield [%][b]	*ee* [%][c]
1[d]	**10a**	Ph	**11a**	91	>99 (*R*)
2	**10b**	4-MeC_6H_4	**11b**	91	>99
3	**10c**	4-$MeOC_6H_4$	**11c**	91	>99
4	**10d**		**11d**	87	99
5	**10e**	3-$MeOC_6H_4$	**11e**	85	96
6	**10f**	2-FC_6H_4	**11f**	88	98
7	**10g**	4-FC_6H_4	**11g**	91	99
8	**10h**	4-ClC_6H_4	**11h**	91	98
9	**10i**	4-BrC_6H_4	**11i**	88	97
10	**10j**	2-naphthyl	**11j**	88	98
11[e]	**10k**		**11k**	87	93

[a] Unless otherwise noted, reactions were carried out with **10** (0.25 mmol) and **2a** (1.5 equiv) in toluene (2.5 mL) at RT. [b] Yield of the isolated product. [c] The enantiomeric excess was determined by HPLC analysis. [d] The absolute configuration of **11a** was determined as *R* by chemical correlation (see the Supporting Information) and the rest of the products were assigned by analogy. [e] The reaction was performed at 0°C.



Scheme 3. Synthesis of α-aminophosphonic acid.

with concentrated HCl to give the desired product in 96% yield.[21]

Conclusion

We have achieved the first highly enantioselective phosphonylation of α,β-unsaturated *N*-acylpyrroles. Excellent yields and enantioselectivities (up to >99% *ee*) were observed for a broad spectrum of both phosphites and *N*-acylpyrroles under mild conditions. Moreover, optically pure α-substituted β- or γ-amino phosphonates can be obtained by several simple transformations of the pyrrolyl phosphonates. The versatility of the *N*-acylpyrrole moiety makes the phosphorus adduct a powerful chiral building block for the synthesis of various phosphonate-containing compounds. Finally, the present strategy can also be applied to the asymmetric hydrophosphonylation of imines in high efficiency (<15 min) and enantioselectivities (93 to >99% *ee*). Further applications of this methodology to the synthesis of biologically and pharmaceutically interesting targets are in progress in our laboratory.

Experimental Section

General procedure for asymmetric hydrophosphonylation of α,β-unsaturated *N*-acylpyrroles: Diethylzinc (0.1 mL, 1 M in toluene, 0.1 mmol) was added to a stirred solution of **L** (32 mg, 0.05 mmol) in toluene (0.5 mL) under an argon atmosphere. The mixture was then stirred at room temperature for 30 min to generate the zinc catalyst. The resulting solution of catalyst was added to a stirred mixture of 4 Å molecular sieves (100 mg, dried at 200 °C under vacuum for 12 h), **1a** (52 mg, 0.25 mmol), and **2a** (48 μL, 0.375 mmol) in toluene (2 mL) at 0 °C under an argon atmosphere. After the addition, the mixture was allowed to warm slowly to room temperature over 12 h. The reaction was quenched with aqueous HCl (1 M) and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate 7:1 to 1:2) to give **3a** (99% yield, >99% *ee*). The optical purity was determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{minor} = 11.5 min, t_{major} = 12.3 min); $[\alpha]_D^{20} = -31$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.38 (m, 2H), 7.38–7.21 (m, 5H), 6.27 (t, J = 2.4 Hz, 2H), 4.18–4.00 (m, 2H), 3.98–3.79 (m, 2H), 3.77–3.60 (m, 1H), 3.60–3.43 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7 (d, J = 18.0 Hz), 135.1 (d, J = 6.8 Hz), 129.1 (d, J = 6.0 Hz), 128.6 (d, J = 2.3 Hz), 127.6 (d, J = 3.0 Hz), 119.0, 113.3, 63.2 (d, J = 7.5 Hz), 62.1 (d, J = 7.5 Hz), 39.5 (d, J = 140.3 Hz), 35.5, 16.3 (d, J = 6.0 Hz), 16.1 (d, J = 5.3 Hz) ppm; ^{31}P NMR (121 MHz, $CDCl_3$): δ = +27.3 ppm; IR (neat): $\tilde{\nu}$ = 2983, 2927, 1719, 1284, 1052, 967, 747, 558 cm^{-1}; HRMS (ESI): m/z calcd for $C_{17}H_{22}NO_4P$: 336.1359 $[M+H]^+$; found: 336.1353.

General procedure for asymmetric hydrophosphonylation of *N*-acylimines: Dimethylzinc (0.167 mL, 1.2 M in toluene, 0.2 mmol) was added to a stirred solution of **L** (64 mg, 0.1 mmol) in toluene (1.83 mL) under an argon atmosphere and the mixture was stirred at room temperature for 0.5 h to generate the zinc catalyst (~0.05 M). The resulting solution of catalyst (0.5 mL, 0.025 mmol) was added to a stirred solution of **10** (0.25 mmol) and **2a** (48 μL, 0.375 mmol) in toluene (2 mL) in one portion at room temperature under an argon atmosphere. After stirring at the same temperature for 15 min, the reaction was quenched with a saturated aqueous solution of NH_4Cl. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate 4:1 to 1:2) to give **11a** (91% yield, >99% *ee*). The optical purity was determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{minor} = 12.1 min, t_{major} = 10.8 min); $[\alpha]_D^{20} = -19$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.80 (m, 3H), 7.59 (d, J = 6.0 Hz, 2H), 7.47 (t, J = 7.5 Hz, 1H), 7.42–7.28 (m, 5H), 5.79 (dd, J = 21.2, 9.5 Hz, 1H), 4.23–4.02 (m, 2H), 4.01–3.86 (m, 1H), 3.79–3.64 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9 (d, J = 7.5 Hz), 135.2, 133.8, 131.6, 128.5 (d, J = 1.5 Hz), 128.3, 128.27 (d, J = 5.3 Hz), 128.0 (d, J = 2.3 Hz), 127.4, 63.3 (d, J = 6.8 Hz), 63.0 (d, J = 7.5 Hz), 50.5 (d, J = 153.8 Hz), 16.4 (d, J = 6.0 Hz), 16.1 (d, J = 6.0 Hz) ppm; ^{31}P NMR (121 MHz, $CDCl_3$): δ = +21.5 ppm; IR (neat): $\tilde{\nu}$ = 3277, 2986, 1650, 1539, 1244, 1026, 699, 562 cm^{-1}; HRMS (ESI): m/z calcd for $C_{18}H_{22}NO_4P$: 348.1359 $[M+H]^+$; found: 348.1349.

Acknowledgements

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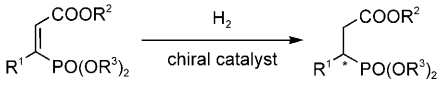

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