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A Facile Cu(I)/TF-BiphamPhos-Catalyzed Asymmetric Approach to Unnatural α-Amino Acid Derivatives Containing *gem*-Bisphosphonates

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Supporting Information

ABSTRACT: A novel catalytic asymmetric Michael addition of azomethine ylide with β-substituted alkylidene bisphosphates was realized in the presence of a chiral copper(I)/TF-BiphamPhos complex. The present system provides a unique and facile access to enantioenriched unnatural α-amino acid derivatives containing *gem*-bisphosphonates (*gem*-BPs) in high yields with excellent diastereoselectivities and enantioselectivities. Subsequent transformations lead to the expedient preparation of biologically active unnatural α-amino acid derivatives containing BPs and bisphosphonic acids without loss of diastereo- and enantiomeric excess.

INTRODUCTION

Optically active nonproteinogenic α-amino acids are useful compounds of great interest and frequently constitute cores of pharmaceutical agents and biologically active compounds.[1] With the rapid development of protein engineering and the discovery of peptide-based drugs, the rational design of nonproteinogenic α-amino acids has attracted considerable attention over the past decades because of their implementation into nonscissile peptide mimics and peptide isosteres.[2] In addition to bioresolution procedures,[3] Ru- and Rh-catalyzed hydrogenation is broadly useful for the asymmetric synthesis of many classes of α-amino acids.[4] The asymmetric Strecker reaction,[5] asymmetric transition-metal-mediated additions of various nucleophiles to α-imino esters,[6] and asymmetric alkylation of benzophenone Schiff base glycine esters using phase-transfer catalysts (PTCs)[7] also provide direct approaches to such compounds and have shown much promise. Despite fruitful growth in this field, the development of more efficient and practical methods for convenient construction of various nonproteinogenic α-amino acids is still challenging and in great demand. Geminal bisphosphonates (*gem*-BPs), which contain a P−C−P moiety, are stable pyrophosphate analogues and constitute an important class of bioactive compounds that has been used for the prevention and treatment of several bone disorders, such as Paget's disease, bone metastasis, myeloma, osteoporosis, and rheumatoid arthritis.[8] Unnatural α-amino acid derivatives containing *gem*-BPs play a significant role in the study of the structure−activity relationship of antineoplastic agents, as exemplified in Figure 1. For example, it has been revealed that the methotrexate (MTX)−BP conjugates possess over 5 times greater antineoplastic activity against osteosarcoma in experimental animal models than MTX alone.[9] 4,4-Bisphosphono-2-(polyhydroxyl-1,2-dihydro-1,2-methanofullerene[60]-61-carboxamido)butyric acid [$C_{60}(OH)_{16}$AMBP], a tissue-vectored bisphosphonate fullerene, confers to bone a stronger affinity for the calcium phosphate mineral hydroxyapatite and hence reduces hydroxyapatite mineralization more efficiently than $C_{60}(OH)_{30}$, which does not contain bisphosphonic acid groups.[10]

Because of the important biological activities and potentially valuable pharmaceutical properties, synthetic methods for *gem*-BPs have been intensively investigated in the past decades. Michael addition of nucleophiles to electron-deficient and highly reactive tetraethyl vinylidenebis(phosphonate) has been established as one of the most efficient approaches for accessing *gem*-BPs.[11] Despite the large body of catalytic asymmetric Michael addition reactions in organic synthesis,[12] tetraethyl alkylidenebis(phosphonate) compounds are underestimated as valuable partners in these reactions, and the limited catalytic asymmetric Michael additions reported for the synthesis of optically active *gem*-BPs containing one formed stereogenic center rely on the use of less sterically hindered and β-unsubstituted tetraethyl vinylidenebis(phosphonate) as the Michael acceptor (Scheme 1 left).[13]

In sharp contrast, tetraethyl alkylidenebis(phosphonate) compounds with β-substituted groups have not been exploited as acceptors in the catalytic asymmetric Michael addition. In view of the simultaneous creation of two adjacent tertiary stereogenic centers, it is a great challenge to obtain both high enantioselectivity and high diastereoselectivity in asymmetric Michael additions

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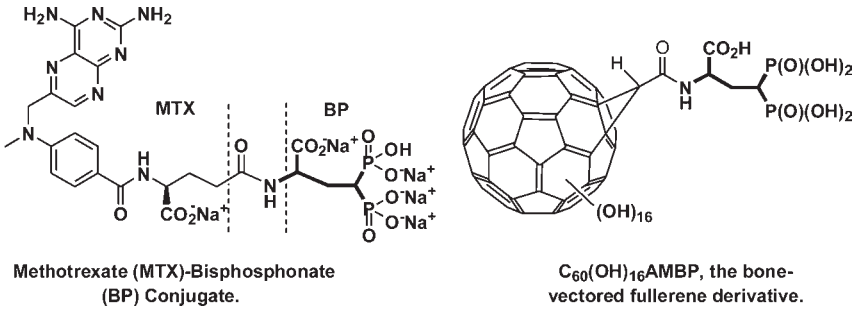
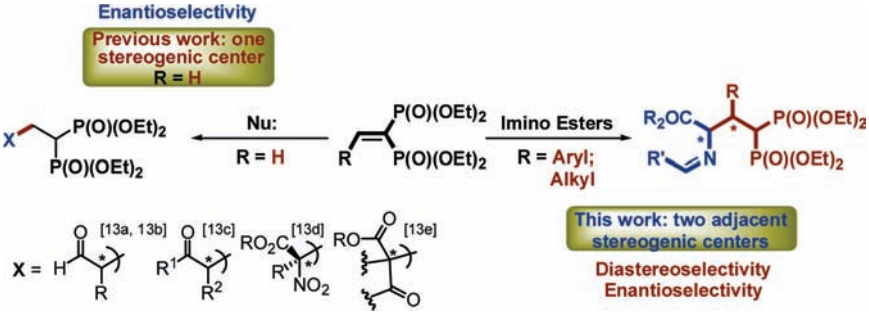


Figure 1. Examples of biologically important molecules containing *gem*-BPs.

Scheme 1. Catalytic Asymmetric Michael Addition for the Synthesis of Optically Active *gem*-BPs Containing One Stereogenic Center (Previous Work) or Two Adjacent Stereogenic Centers (This Work)



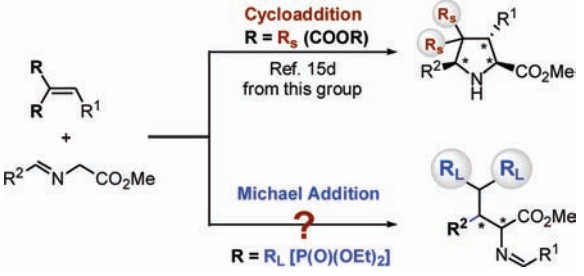
involving β-substituted tetraethyl vinylidenebis(phosphonate) compounds. Herein we describe the first catalytic asymmetric Michael additions of glycine imino esters[7a,e,14] to various β-substituted tetraethyl alkylidenebis(phosphonate) compounds using the Cu(I)/TF-BiphamPhos complex,[15] which provide unnatural α-amino acid derivatives containing *gem*-BPs in good yields with excellent diastereoselectivity and enantioselectivity (Scheme 1 right).

RESULTS AND DISCUSSION

This work was inspired by our recent finding that the reaction of alkylidenemalonates with azomethine ylides in the presence of Ag(I)/TF-BiphamPhos gives 1,3-dipolar cycloadducts[15d] rather than Michael adducts, although the latter are the common products of most asymmetric reactions involving alkylidenemalonates (Scheme 2).[16] We envisioned that introducing bulkier BP groups next to the corresponding alkylidene moiety would efficiently suppress the cycloaddition route, which would be disfavored because of steric hindrance, and hence facilitate the formation of unnatural α-amino acid derivatives containing *gem*-BPs via Michael addition.

To test this idea, we first examined and compared the reactivities of methyl cinnamylate (**3**), diethyl benzylidenemalonate (**4**), 2-(diethoxyphosphoryl)-3-phenylacrylic acid ethyl ester (**5**), tetraethyl benzylidenebis(phosphonate) (**6a**), and diethyl benzylidenephosphonate (**7**) with *N*-benzylidene glycine methyl ester (**2a**) under the previously reported[15d] optimal reaction conditions for asymmetric 1,3-dipolar cycloaddition (1,3-DC) of alkylidenemalonates, except that *rac*-(±)-TF-BiphamPhos (**1a**) was used as the ligand (Scheme 3). The 1,3-DC pathway occurred exclusively with monoactivated **3** and

Scheme 2. Proposed Asymmetric Michael Addition for the Construction of Unnatural α-Amino Acid Derivatives Containing the *gem*-BP Motif



bisactivated **4**, leading to excellent diastereoselectivity. Replacing one of the less bulky ethoxycarbonyl groups in **4** with a much bulkier $P(O)(OEt)_2$ group in **5** still gave rise to cycloadducts **10** and **11**, albeit with low diastereoselectivity. However, the 1,3-DC pathway was suppressed and the Michael addition (MA) pathway occurred with excellent diastereoselectivity (>99:1) when both of the less bulky CO_2Et groups in **4** were replaced with the bulkier $P(O)(OEt)_2$ groups in **6a**. On the contrary, no reaction occurred with the corresponding monoactivated phosphonate **7** under the same reaction conditions, which indicates that two bulkier phosphonate groups on the β-substituted olefin (**6a**) are required for this transition-metal-catalyzed Michael addition reaction to occur. The vinylphosphonate showed much lower reactivity, a finding also noticed by Alexakis and co-workers[13a,b] in the organocatalyzed asymmetric Michael addition of aldehyde to β-unsubstituted vinylphosphonates.

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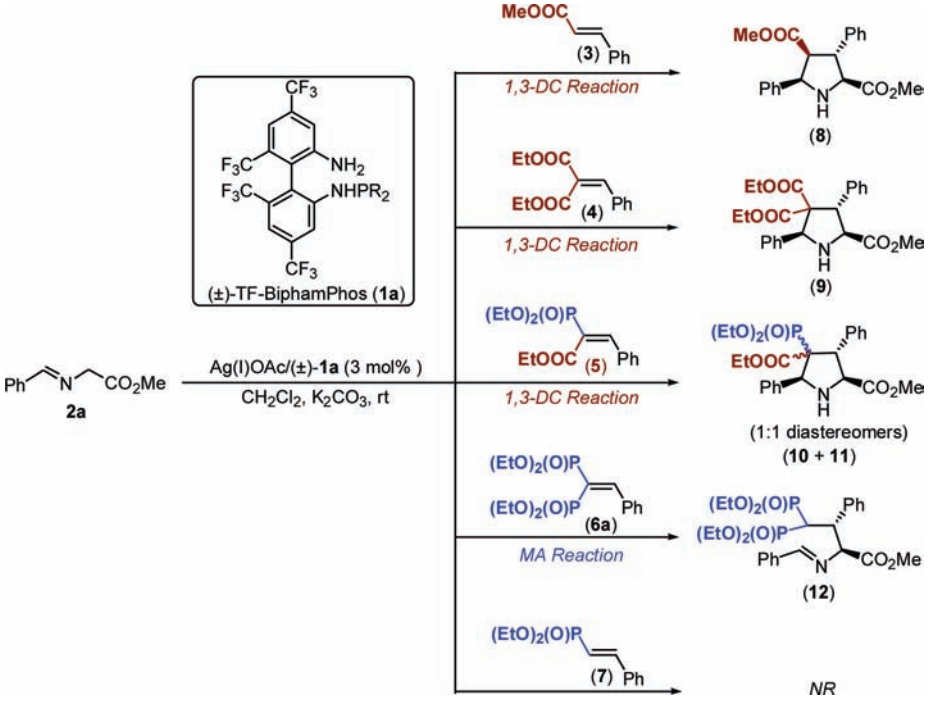
Scheme 3. Reaction Pathway and Reactivity Studies of *β*-Substituted Vinylcarboxylate 3, *β*-Substituted Vinylidenebis(carboxylate) 4, *β*-Substituted Vinylidenecarboxylate−phosphonate 5, *β*-Substituted Vinylidenebis(phosphonate) 6a, and *β*-Substituted Vinylphosphonate 7



Asymmetric Michael Addition To Construct the Optially Active *gem*-BP Motif. Having established the substrate-controlled Michael addition reaction pathway exerted by the *gem*-BP group on the *β*-substituted olefin, we then conducted the novel asymmetric reaction to evaluate the enantioselectivity with chiral TF-BiphamPhos ligand. To our delight, the reaction of tetraethyl benzylidenebis(phosphonate) **6a** with *N*-benzylidene glycine methyl ester **2a** catalyzed by Ag(I)/(*S*)-TF-BiphamPhos [(*S*)-**1a**] indeed gave the desired Michael adduct **12** in 82% yield with remarkable diastereoselectivity (99:1) and 30% enantioselectivity within 3 h at room temperature.[17] Encouraged by this positive result, we screened various metal salts to examine the effect of different Lewis acids. Representative results are summarized in Table 1. Though gold(I) proved to be inactive in this transformation (Table 1, entry 2), $Cu(CH_3CN)_4BF_4$ combined with ligand (*S*)-**1a** showed high reactivity and better enantioselectivity: the reaction was finished within less than 15 min, affording the desired sole adduct in 95% yield with 77% ee (entry 3). Subsequent ligand screening revealed that TF-BiphamPhos **1e** bearing bromines at the 3 and 3′ positions of the TF-BIPHAM backbone was the most effective chiral ligand, providing **12** as the sole product in high yield and 84% ee (entry 7; see the Supporting Information for more details). The choice of solvent was also important: CH_2Cl_2 and $CHCl_3$ were identified as the most suitable solvents (entries 7 and 13). The effect of the ratio of chiral ligand to $Cu(CH_3CN)_4BF_4$ on the enantioselectivity was also examined. The catalysts prepared from $Cu(CH_3CN)_4BF_4$ and **1e** in 1:1 and 1:2 ratios showed similar results for the yields and enantioselectivities (entries 7 and 14). Reducing the temperature to −20 °C in CH_2Cl_2 led to completion of the reaction with 94% ee in less than 30 min (entry 15). Access to both enantiomers was found to be possible with the same level of enantioselectivity (entries 15 and 16). The catalyst loading was successfully reduced to 1 mol % without any loss of reactivity or enantioselectivity (entry 17). Even when the catalyst loading was reduced to 0.1 mol %, comparable results (57% yield and 94% ee) were still achieved with extended reaction time (entry 18).

Since the acidity of the C(α)−H bond in the glycine imino ester is affected by a resonance-assisted hydrogen bond,[18] the electronic and steric properties of the glycine imino ester were tuned for further optimization, and the results are summarized in Table 2. To simplify the determination of the enantiomeric excess, different Michael adducts with respect to the Schiff base moiety could be easily transferred into the deprotected product **13a**[19] and then analyzed under the same HPLC separation conditions. Generally, aromatic aldehyde-derived imino esters gave higher enantioselectivities and reactivities than aliphatic ones (Table 2, entries 1−8), and the latter afforded only trace amounts of product even at room temperature after 48 h (entry 9). The electronic property of the substituent on the aryl ring has significant effect on this transformation: an electron-deficient substituent at the para position of the phenyl ring led to the same selectivity and reactivity as the model substrate (entries 2 and 3), whereas an ortho substituent had a negative effect on the enantioselectivity, probably caused by the disfavored steric congestion (entries 6 and 7). In contrast, electron-rich aromatic aldehyde derivatives displayed remarkably decreased reactivity, especially the *p*-methoxybenzaldehyde derivative, for which a yield of only 46% was achieved in 48 h at −20 °C, although the enantioselectivity was kept at the same level (entry 5). Benzophenone Schiff base could not be employed in this transformation (entry 10), probably because of the reduced acidity of the C(α)−H bond in the corresponding imino ester.[20] The different reactivities and stereoselectivities of those glycine imino esters

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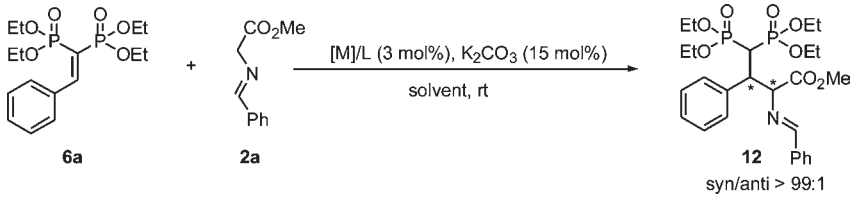
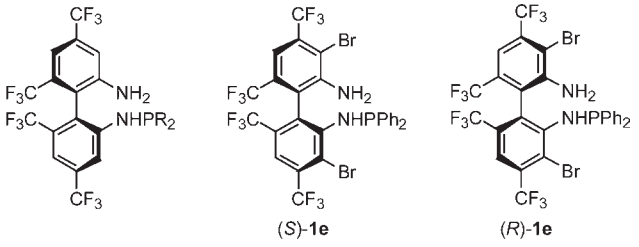
Table 1. Screening Studies of the Asymmetric Michael Addition of Imino Ester 2a and Tetraethyl Benzylidenebis(phosphonate) 6a[a]



entry	TF-BiphamPhos[b]	[M]	solvent	T (°C)	time (min)	yield (%)[c]	ee (%)[d]
1	(*S*)-**1a**	AgOAc	CH_2Cl_2	rt	180	82	30
2	(*S*)-**1a**	Au(*c*-HexNC)$_2$BF$_4$	CH_2Cl_2	rt	180	–	–
3	(*S*)-**1a**	Cu(CH$_3$CN)$_4$BF$_4$	CH_2Cl_2	rt	15	95	77
4	(*S*)-**1b**	Cu(CH$_3$CN)$_4$BF$_4$	CH_2Cl_2	rt	300	87	8
5	(*S*)-**1c**	Cu(CH$_3$CN)$_4$BF$_4$	CH_2Cl_2	rt	300	75	10
6	(*S*)-**1d**	Cu(CH$_3$CN)$_4$BF$_4$	CH_2Cl_2	rt	300	86	32
7	(*R*)-**1e**	Cu(CH$_3$CN)$_4$BF$_4$	CH_2Cl_2	rt	15	90	84
8	(*R*)-**1e**	Cu(CH$_3$CN)$_4$BF$_4$	PhMe	rt	180	83	57
9	(*R*)-**1e**	Cu(CH$_3$CN)$_4$BF$_4$	THF	rt	90	85	63
10	(*R*)-**1e**	Cu(CH$_3$CN)$_4$BF$_4$	hexene	rt	120	87	53
11	(*R*)-**1e**	Cu(CH$_3$CN)$_4$BF$_4$	EtOAc	rt	180	86	64
12	(*R*)-**1e**	Cu(CH$_3$CN)$_4$BF$_4$	acetone	rt	180	85	72
13	(*R*)-**1e**	Cu(CH$_3$CN)$_4$BF$_4$	$CHCl_3$	rt	15	84	84
14[e]	(*R*)-**1e**	Cu(CH$_3$CN)$_4$BF$_4$	$CHCl_2$	rt	15	86	84
15	(*R*)-**1e**	Cu(CH$_3$CN)$_4$BF$_4$	CH_2Cl_2	−20	30	92	94
16	(*S*)-**1e**	Cu(CH$_3$CN)$_4$BF$_4$	CH_2Cl_2	−20	30	90	95
17[f]	(*R*)-**1e**	Cu(CH$_3$CN)$_4$BF$_4$	CH_2Cl_2	−20	30	91	94
18[g]	(*R*)-**1e**	Cu(CH$_3$CN)$_4$BF$_4$	CH_2Cl_2	−20	2880	57	94

[a] All of the reactions were carried out with 0.23 mmol of **6a** and 0.35 mmol of **2a** in 2 mL of solvent. [b] Structures of the ligands are shown below. [c] Isolated yields. [d] Determined by HPLC analysis. [e] $CuBF_4$ (3 mol %) and (*R*)-**1e** (6 mol %). [f] Run with 1 mol % catalyst. [g] Run with 0.1 mol % catalyst.



(*S*)-**1a**: R = Ph;
(*S*)-**1b**: R = 3,5-bis(methyl)phenyl,
(*S*)-**1c**: R = 3,5-bis-(trifluoromethyl)phenyl,
(*S*)-**1d**: R = Cy;

indicate that this Michael addition was affected not only by the acidity of the C(α)−H bond in the glycine imino ester but also by the steric hindrance and electronic effect of the imino moiety in the glycine imino ester. It could not be ascribed to the reversibility of this asymmetric Michael addition reaction because a ^{31}P NMR investigation showed that this reaction is not reversible (see the Supporting Information for details).

Under the optimal reaction conditions, a series of representative β-substituted alkylidenebis(phosphonate) compounds were next explored to examine the substrate scope and limitation of this novel Michael addition. As shown in Table 3, alkylidenebis(phosphonate) compounds bearing electron-rich (entries 3−5), electron-neutral (entries 1, 2, and 13), or electron-deficient groups (entries 6−12) on the aryl rings reacted smoothly with glycine methyl ester **2a**, exclusively affording the corresponding adducts (**13a**−**l**) in high yields (85−95%) with good enantioselectivities (93−99%) at −20 °C within 0.5 h. The substitution pattern and electronic property of the phenyl ring had little effect on the enantioselectivity. It is noteworthy that comparable excellent performance was still achieved for the sterically hindered *o*-chloro-substituted BP **6f** in terms of diastereo- and enantioselectivity and reactivity (entry 7). Additionally, heteroaryl-substituted alkylidenebis(phosphonate) **6m** derived from 2-furylaldehyde also worked well in this transformation, leading

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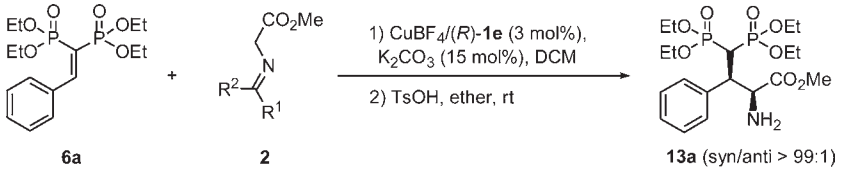
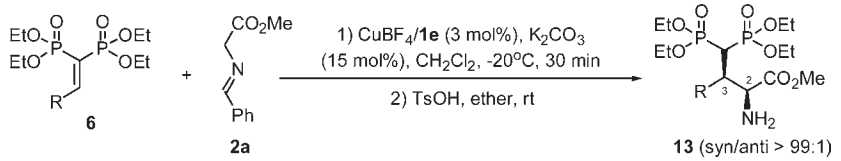
Table 2. Influence of the Imino Ester 2 in the Cu(I)-Catalyzed Asymmetric Michael Addition of Tetraethyl Benzylidenebis(phosphonate) 6a[a]



entry	R^1	R^2	T (°C)	time (min)	yield (%)[b]	ee (%)[c]
1	Ph (**2a**)	H	−20	30	90	94
2	*p*-F-Ph (**2b**)	H	−20	30	88	94
3	*p*-Br-Ph (**2c**)	H	−20	30	91	94
4	*p*-Me-Ph (**2d**)	H	−20	30	88	92
5	*p*-MeO-Ph (2e)	H	−20	1440	46	95
6	*o*-Me-Ph (**2f**)	H	−20	30	85	83
7	*o*-Cl-Ph (**2g**)	H	−20	30	89	84
8	2-naphthyl (**2h**)	H	−20	30	78	80
9	cyclohexyl (**2i**)	H	rt	2880	50	92
10	Ph (**2j**)	Ph	−20	30	–	–

[a] All of the reactions were carried out with 0.23 mmol of **6a** and 0.35 mmol of **2** in 2 mL of solvent. [b] Isolated yields. [c] Determined by HPLC analysis.

Table 3. Substrate Scope of Cu(I)-Catalyzed Asymmetric Michael Additions of Imino Ester 2a and Various β-Substituted Alkylidenebis(phosphonates) 6[a]



entry	ligand	R	13	yield (%)[b]	ee (%)[c]
1	(*R*)-**1e**	Ph (**6a**)	**13a**	90	94
2	(*S*)-**1e**	Ph (**6a**)	**13a**	85	95
3	(*R*)-**1e**	*p*-Me-Ph (**6b**)	**13b**	92	99
4	(*R*)-**1e**	*m*-Me-Ph (**6c**)	**13c**	90	95
5	(*R*)-**1e**	*p*-MeO-Ph (**6d**)	**13d**	95	97
6	(*R*)-**1e**	*p*-Cl-Ph (**6e**)	**13e**	85	95
7	(*R*)-**1e**	*o*-Cl-Ph (**6f**)	**13f**	90	96
8	(*R*)-**1e**	*m*-Cl-Ph (**6g**)	**13g**	88	98
9	(*R*)-**1e**	*p*-F-Ph (**6h**)	**13h**	90	99
10	(*R*)-**1e**	*p*-Br-Ph (**6i**)	**13i**	89	95
11	(*R*)-**1e**	*p*-CF_3−Ph (**6j**)	**13j**	88	95
12	(*R*)-**1e**	*p*-NO_2−Ph (**6k**)	**13k**	91	93
13	(*R*)-**1e**	2-naphthyl (**6l**)	**13l**	85	96
14	(*R*)-**1e**	2-furyl (**6m**)	**13m**	82	96
15	(*R*)-**1e**	Me (**6n**)	**13n**	71	95
16	(*R*)-**1e**	Et (**6o**)	**13o**	76	95
17	(*R*)-**1e**	Pr (**6p**)	**13p**	73	95
18	(*R*)-**1e**	$CyCH_2$ (**6q**)	**13q**	72	89
19	(*R*)-**1e**	^{i}Bu (**6r**)	**13r**	70	90
20	(*R*)-**1e**	H (**6s**)	**13s**	75	89

[a] All of the reactions were carried out with 0.23 mmol of **6** and 0.35 mmol of **2a**. [b] Isolated yields of **13a**−**m** and the corresponding benzoylated compounds **13n**−**s** using β-aryl-substituted (entries 1−14) and β-alkyl-substituted (entries 15−20) alkylidenebis(phosphonate) compoundss, respectively, as acceptors. [c] Determined by HPLC analysis.

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to 82% yield and 96% ee (entry 14). Remarkably, the alkyl-substituted alkylidenebis(phosphonate) compounds derived from both linear (**6n**−**p**) and branched (**6q** and **6r**) aliphatic aldehydes proved to be excellent substrates with respect to diastereoselectivity and enantioselectivity (entries 15−19). The less bulky Michael acceptor tetraethyl vinylidenebis-(phosphonate) (**6s**) was also tested in this catalytic system, and a good yield and ee (89%) were also achieved for the desired adduct, which contains one newly formed stereogenic center (entry 20).

The relative and absolute configuration of **13a** produced using $CuBF_4$/(*R*)-TF-BiphamPhos [(*R*)-**1e**] was unequivocally determined to be (2*S*,3*R*) by X-ray diffraction analysis (Figure 2; see the Supporting Information for more details). Those of other adducts were deduced on the basis of this result.

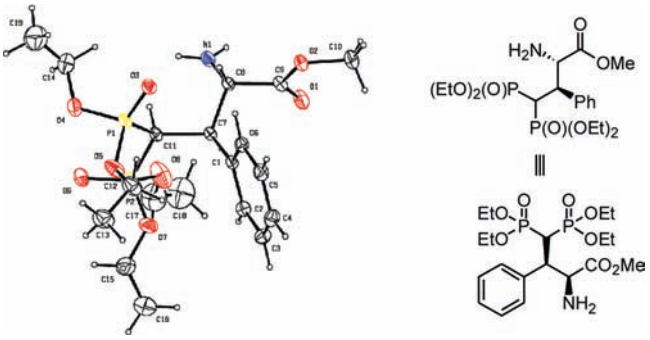

Figure 2. X-ray crystal structure of (2*S*,3*R*)-**13a**.

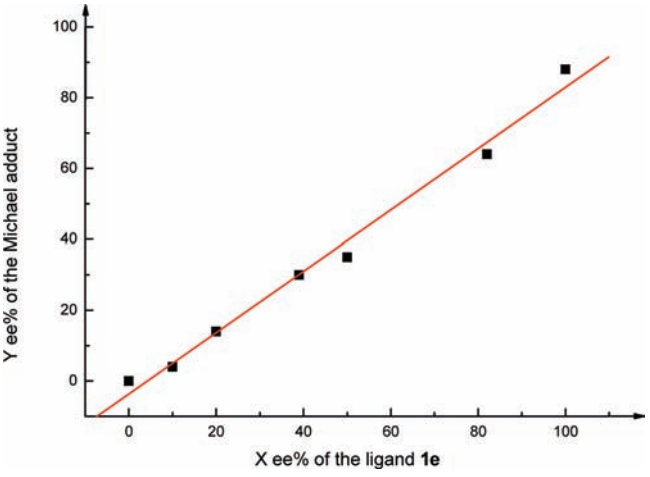

Figure 3. Linear correlation of the adduct and ligand ee's in the asymmetric Michael addition of **2a** to **6a** catalyzed by Cu-$(CH_3CN)_4BF_4$/(*S*)-**1e**.

Reaction Mechanism. In order to gain mechanistic insight into the nature of the possible active species formed in this highly efficient catalytic system, the relationship between the ee values for the Michael adduct and the ee values for the chiral ligand was also examined. As shown in Figure 3, with TF-BiphamPhos (*S*)-**1e** as the chiral ligand, we observed a clear linear effect in the asymmetric Michael addition of **2a** to **6a**. Such a linear correlation between the product ee and the ligand ee indicates that the possible active species in this highly efficient Cu(I)/TF-Biphamphos-catalyzed Michael addition reaction is a monomeric Cu(I) complex having (*S*)-TF-BiphamPhos as a bidentate chiral ligand [Cu(I):**1e** = 1:1].[21]

The significant role played by the amino group of the chiral TF-BiphamPhos ligand in this catalytic system was further demonstrated through a control experiment using the chiral ligand (*R*)-**1f**, in which the amino group connected to the upper aryl ring had been removed according to the synthetic route from the chiral backbone (*S*)-TF-BIPHAM[22] in four steps (Scheme 4). Under the optimized reaction conditions but with (*R*)-**1f** as the ligand, the Michael addition of **2a** to **6a** became very sluggish, and the corresponding Michael adduct **12** was formed in 85% yield with only 7% ee even after 24 h, although the diastereoselectivity was still kept at the same high level. This indicates that the NH_2 moiety of the chiral TF-BiphamPhos indeed plays a great role in this asymmetric Michael addition reaction.

According to the previous literature, this asymmetric Michael addition reaction could be explained through the proposed transition state illustrated in Figure 4. The in situ-formed azomethine ylide is coordinated to the copper center of the active species bearing (*S*)-TF-BiphamPhos as the chiral ligand and oriented in the favored tetracoordinated transition state[23] because of the steric repulsion between the phenyl group in the ylide and the phenyl ring on the phosphorus atom of the chiral ligand. The high steric congestion imposed by the latter effectively blocks the approach of **6a** from the back side of the coordinated azomethine ylide, giving instead the Michael adduct **13a** in the (2*R*,3*S*) configuration through front-side attack. Therefore, the opposite enantiomer, (2*S*,3*R*)-**13a**, is generated from the corresponding active Cu(I) species having (*R*)-TF-BiphamPhos as the chiral ligand. The phosphonate group of **6a** can coordinate to the Cu(I) center, which can stabilize the negatively charged oxygen atom in the proposed transition state.[23] We cannot rule out the possible hydrogen-bonding interaction between the phosphonate group and the NH_2 group of the chiral ligand, which also could facilitate stabilization of the proposed transition state.[24]

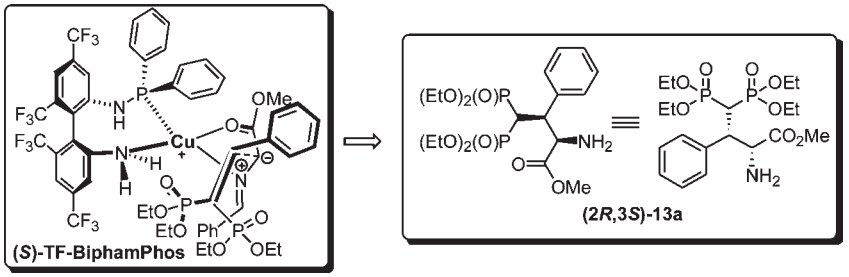

Figure 4. Proposed transition state leading to the syn Michael adduct (2*R*,3*S*)-**13a** with the Cu(I)/(*S*)-**1a** Complex.

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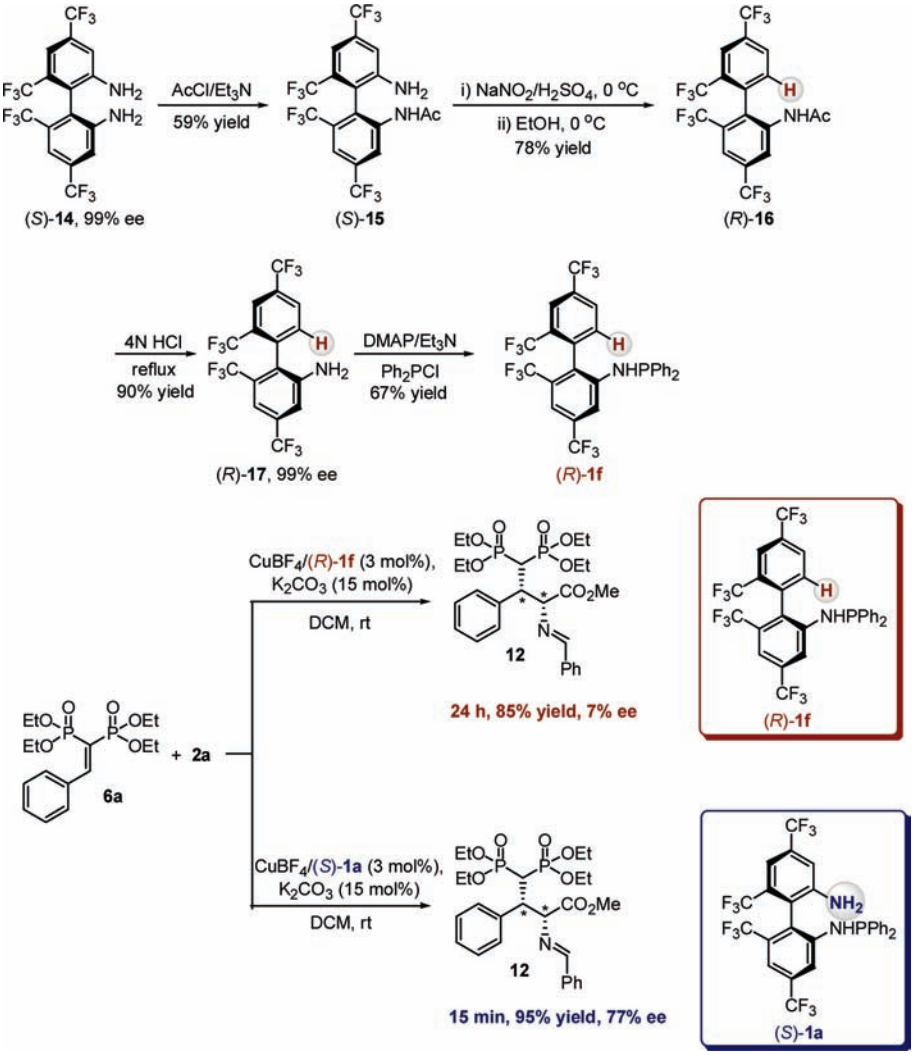
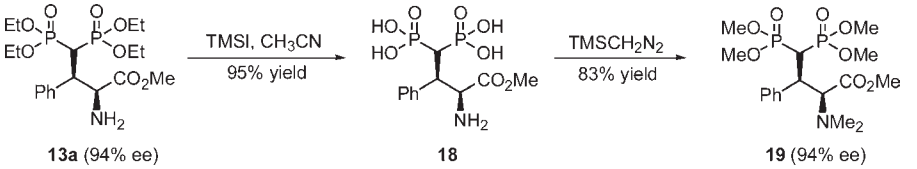
Scheme 4. Synthesis of Chiral Ligand 1f and Control Experiments To Evaluate the Role of the NH_2 Group of the TF-BiphamPhos Ligand in the Asymmetric Michael Addition Reaction



Scheme 5. Cleavage of the Tetraethyl Group in Michael Adduct 13a for the Synthesis of Bisphosphonic Acid 18



Synthetic Transformation of the Michael Adduct. To illustrate the utility of this novel Michael addition, transformations of the optically active adduct **13a** containing the *gem*-BP group were subsequently investigated. The biologically active bisphosphonic acid **18**, which constitutes a core component of various biologically active compounds,[9,10,25] was easily attained through cleavage of the tetraethyl group in the BP moiety of **13a** with TMSI[26] at room temperature in quantitative yield without loss of diastereo- and enantiomeric excess, as confirmed by the fact that the same ee value was measured for tetramethyl bisphosphonate **19**, which was obtained in turn by simultaneous esterification and methylation of **18** with trimethylsilyl diazomethane (Scheme 5).

On the other hand, α-fluorinated and -chlorinated compounds **21** and **22**, which are analogues of monohalogenated methylenebis(phosphonate) compounds,[27] were easily obtained by benzoylation and subsequent halogenation via treatment of the corresponding carbanion of **20** with Selectfluor and *N*-chlorosuccinimide (NCS), respectively (Scheme 6).[26] A hydroxyl group could be also be directly introduced into the BP moiety, forming the corresponding optically active α-hydroxybis(phosphonate) **23**. This methodology offers a unique and facile access to derivatives

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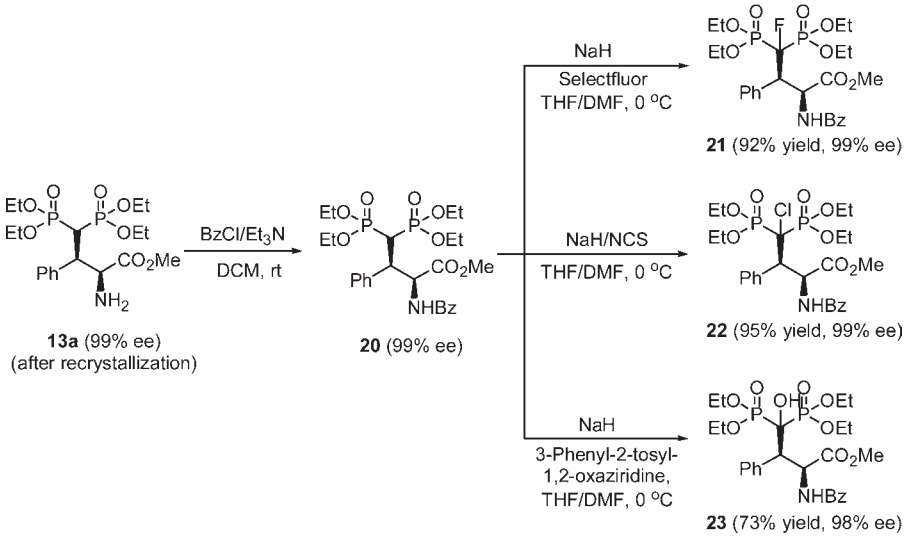
Scheme 6. α-Fluorinated, -Chlorinated, and -Hydroxylated Bisphosphonate Derivatives of Michael Adduct 13a



of unnatural α-amino acids[1] containing *gem*-BPs and bisphosphonic acids,[8] which is expected to find valuable applications in medicinal chemistry.

CONCLUSION

In summary, we have successfully developed the first example of the catalytic synthesis of enantiomerically enriched unnatural α-amino acid derivatives containing *gem*-BPs by realizing the direct asymmetric Michael addition of azomethine ylides to tetraethyl alkylidenebis(phosphonate) compounds under mild conditions. The highly efficient Cu-$(CH_3CN)_4BF_4$/TF-BiphamPhos catalytic system exhibited excellent performance, providing the nonproteinogenic α-amino acid derivatives containing *gem*-BPs in good yields with excellent diastereoselectivities (>99:1) and high enantioselectivities (89−99% ee), and subsequent transformations led to the expedient preparation of biologically active BPs and bisphosphonic acids.

ASSOCIATED CONTENT

Supporting Information. Complete refs 11a and 11c, experimental procedures, compound characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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