Communication

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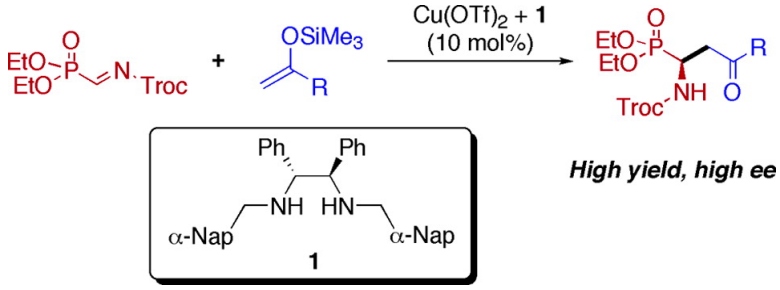

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Catalytic Asymmetric Synthesis of α-Amino Phosphonates Using Enantioselective Carbon−Carbon Bond-Forming Reactions

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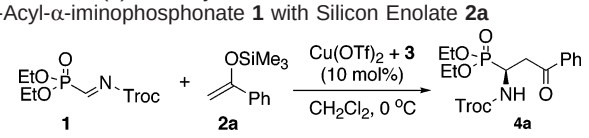
α-Amino phosphonates are key compounds as analogues of α-amino acids in medicinal chemistry and pharmaceutical sciences.[1] Despite the importance of optically active α-amino phosphonates, methods to synthesize them are limited.[2] Schöllkopf et al.[2a] and Steglich et al.[2b] reported highly diastereoselective synthetic methods, respectively, where the use of stoichiometric amounts of chiral auxiliaries were needed. Shibasaki et al.[2c,d] reported the first catalytic asymmetric hydrophosphonylation of imines using lanthanide-potassium-BINOL heterobimetallic complexes. In this communication, we describe an alternative approach to α-amino phosphonates via enantioselective carbon−carbon bond-forming reactions: addition of silicon enolates to *N*-acyl α-iminophosphonates catalyzed by a chiral copper(II) complex. The synthesis of biologically important, optically active *β*-carboxyl-α-aminophosphonic acid derivatives is also described.

N-Acyl-α-iminophosphonate **1** (Troc = 2,2,2-trichloro-ethoxycarbonyl) was prepared by a modified Steglich method,[2b] in which a polymer-supported amine was used instead of the Hünig base.[3] We then conducted the reaction of **1** with a silicon enolate (**2a**) derived from acetophenone in the presence of a copper(II) complex derived from $Cu(OTf)_2$ and diamine **3**. The reaction proceeded smoothly to afford the desired adduct **4a** in high yield, albeit with moderate enantioselectivity. We have previously used the same copper complex for the activation of α-imino esters, and high yields and enantioselectivity were obtained.[4] Compared with α-imino esters, *N*-acyl-α-iminophosphonates have stronger Lewis basicity,[2c] and thus, coordination of **1** to the Cu catalyst is presumed to be stronger. Therefore, release of the Cu catalyst from the product was assumed to be slow, thus allowing the background reaction to take place in the absence of a catalyst serving to reduce overall enantioselectivity (*vide infra*).

To address this issue, we screened several proton sources expected to release the catalyst from the product; we found that hexafluoroisopropyl alcohol (HFIP) was suitable for our purpose.[5] When one equivalent of HFIP was added to the reaction system, the reaction of **1** with **2a** also proceeded smoothly to afford the desired product **4a** in high yield with slight improvement of enantioselectivity (Table 1, entry 2). Moreover, it was found that the selectivity was further improved when the substrates, **1** and **2a**, were slowly added to a solution of the catalyst over 8 h (entries 3−6). Conducting the reaction in the presence of HFIP (2 equiv) and MS 3A (50 mg/mmol), addition of substrates to the catalyst solution, over 8 h, gave the best result (86% yield, 91% ee).[6] Interestingly, the same levels of yield and enantioselection were obtained when the substrates were added to the catalyst over 48 h without HFIP (entry 7).

Having determined the optimal conditions (Table 1, entry 6), other silicon enolates were examined, the results are summarized in Table 2. Silicon enolates derived from various aromatic and aliphatic ketones worked well to afford the corresponding adducts in high yields (70−88%) with high enantioselectivities (76−94% ee) in all cases (entries 1−11). On the other hand, in the reaction with silicon enolate **2l** derived from the thioester, it was found that decomposition of **2l** in the presence of HFIP decreased the yield of the desired product. We then decided to use the slow addition of the substrates to the catalyst without HFIP. The enantioselectivity increased as the addition time was prolonged, and when the

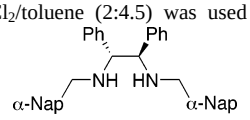
Table 1. Cu(II)-**3**-Catalyzed Reactions of *N*-Acyl-α-iminophosphonate **1** with Silicon Enolate **2a**



1 **2a** **4a**

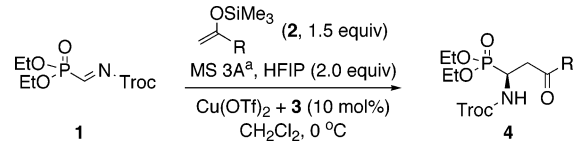
entry	additive	yield (%)	ee (%)
1[a]	−	78	49
2[a]	HFIP (1.0 equiv)	87	65
3[b]	HFIP (1.0 equiv)	81	89
4[b,c]	HFIP (1.0 equiv)	78	93
5[b,c]	HFIP (2.0 equiv)	82	92
6[b,c]	HFIP (2.0 equiv), MS 3A (50 g/mol)	86	91
7[d]	MS 3A (50 g/mol)	82	93

[a] **1** was slowly added over 0.5 h. [b] **1** was slowly added over 8 h. [c] **2a** was slowly added over 8 h. [d] **1** and **2a** were slowly added over 48 h simultaneously. CH_2Cl_2/toluene (2:4.5) was used as a solvent system.



3

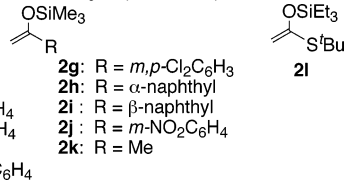
Table 2. Cu(II)-**3**-Catalyzed Reactions of **1** with Various Kinds of Silicon Enolates **2**



1 **4**

entry[b]	enolate	product	yield (%)	ee (%)	entry[b]	enolate	product	yield (%)	ee (%)
1	**2a**	**4a**	86	91	7	**2g**	**4g**	83	92
2	**2b**	**4b**	82	85	8	**2h**	**4h**	79	92
3	**2c**	**4c**	71	91	9	**2i**	**4i**	84	87
4	**2d**	**4d**	86	86	10	**2j**	**4j**	88	94
5	**2e**	**4e**	80	89	11	**2k**	**4k**	70	89
6	**2f**	**4f**	82	76	12[c]	**2l**	**4l**	69	90

[a] 50 g/mol. [b] **1** and **2** were slowly added over 8 h. [c] In the absence of HFIP, **1** and **2l** were slowly added over 48 h. CH_2Cl_2/toluene (2:4.5) was used as a solvent system, and catalyst (15 mol %) was used.



2a: R = Ph
2b: R = *p*-Tol
2c: R = *p*-Cl C_6H_4
2d: R = *p*-Br C_6H_4
2e: R = *p*-IC_6H_4
2f : R = *p*-MeOC_6H_4
2g: R = *m,p*-$Cl_2C_6H_3$
2h: R = α-naphthyl
2i : R = β-naphthyl
2j : R = *m*-$NO_2C_6H_4$
2k: R = Me

2l

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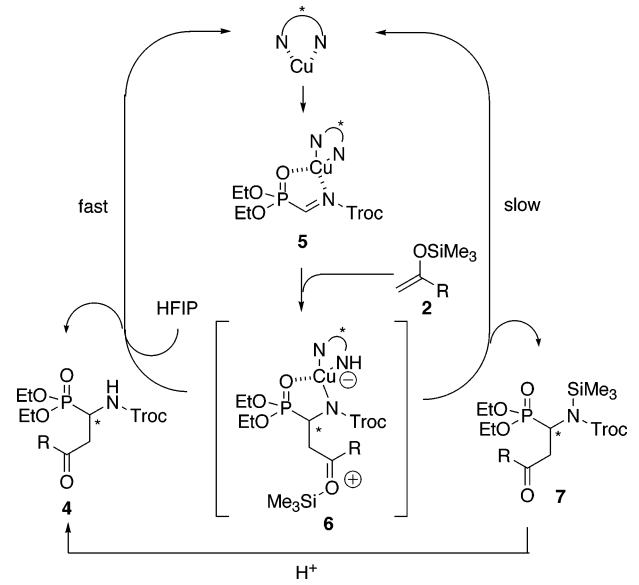
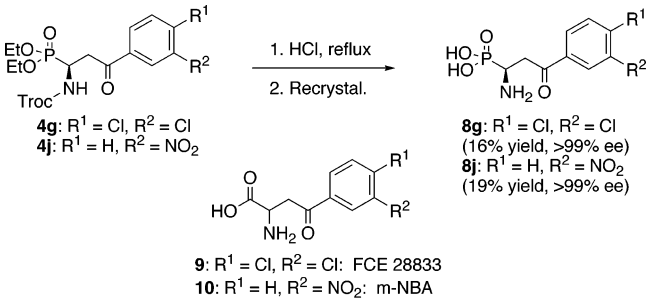
Scheme 1. Proposed Catalytic Cycle



Scheme 2. Synthesis of **8g** and **8j**

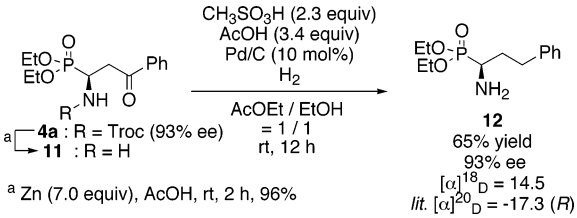


substrates were added over 48 h to the catalyst, the enantioselectivity was improved to be 90%.

Scheme 1 shows the proposed catalytic cycle. The copper(II)−diamine complex is assumed to activate **1** to attack silicon enolates via a bidentate coordination mode (**5**) to form intermediate **6**. The key for completion of the catalytic cycle is the release of the catalyst from **6**, and it is assumed that this process would be slow due to the high basicity of **1**. When HFIP was added, intermediate **6** reacted with HFIP to form the product **4** along with regeneration of the Cu catalyst; the adduct **7** was not observed at all. On the other hand, in the absence of HFIP, when the substrates **1** and **2** were slowly added to the catalyst, silicon transfer process from **6** to **7** occurred slowly to release the catalyst from **6**. In the experiments, N-silylated adduct **7** was obtained as a major product. In addition, it is noteworthy that, in the absence of any copper complex when **1** and **2** were combined over 1 min even at −78 °C, the reaction proceeded rapidly to give **4a**. Considering these results, the slow addition of the substrates to the catalyst is preferable for the asymmetric induction.

The products obtained in this reaction are β-carboxyl-α-aminophosphonic esters, phosphorus analogues of aspartic acid,[7] which have potentially interesting bioactivity. γ-Keto-α-amino acid derivatives **9** (FCE28833) and **10** (*m*-NBA) are kynurenine 3-hydroxylase inhibitors.[8] We prepared their phosphorus analogues **8g** and **8j** from **4g** and **4j**, respectively (see Scheme 2).[9] On the other hand, the adduct **4a** was transformed into α-aminophosphonate **12**, an intermediate for the synthesis of inhibitors of endothelin-converting enzymes (see Scheme 3).[10] It is noted that these biologically interesting compounds can be readily prepared using this catalytic asymmetric reaction.

Scheme 3. Synthesis of **12**



In summary, we have developed a highly enantioselelctive reaction of silicon enolates with *N*-acyl-α-iminophosphonates leading to nonracemic α-amino phosphonates. A copper (II) complex was shown to be effective catalysts for this reaction, giving high yields and selectivities. It is noteworthy that this reaction opens a new pathway to various biologically important, nonracemic α-amino phosphonate derivatives. Studies into substrate variation, allowing access to libraries of α-amino phosphonates, and the application of this catalytic procedure to other reactions of *N*-acyl-α-iminophosphonates are currently underway in our laboratory.

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Supporting Information Available: Experimental section (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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