Asymmetric Synthesis

Stereospecific, Enantioselective Allylation of α-Hydrazono Esters by Using Allyltrichlorosilanes with BINAP Dioxides as Neutral-Coordinate Organocatalysts**

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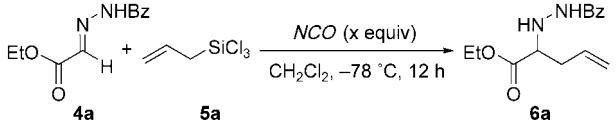
Enantioselective allylation of α-imino esters or their equivalents provides one of the most efficient routes to optically active natural and unnatural α-amino acids. Lectka et al. reported enantioselective allylation of a hemiacetal of a *N*-sulfonyl α-imino ester with trimethyl(2-phenylallyl)silane and related silanes using a chiral Cu^{I} catalyst.[1] Jørgensen et al. also reported at almost the same time that the chiral Cu^{I} catalyst had lower activity for the reaction with allylsilanes. His group used allylstannanes instead of allylsilanes.[2] However, in both cases, the enantioselectivities obtained were still unsatisfactory, and were dependent on the structure of allylsilanes. Recently, our group also reported that enantioselective allylation of α-hydrazono esters with allyltrimethoxysilanes proceeded smoothly in aqueous media in the presence of a ZnF_2-chiral diamine complex.[3] However, also in this case the enantioselectivities obtained were less than 90% *ee*. Furthermore, only a few examples of diastereo- and enantioselective addition of γ-substituted allyl metals to α-imino esters have been reported;[1b,2,4] no *stereospecific,* enantioselective allylation has been attained to date.

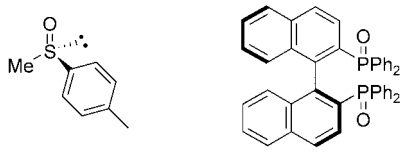
Recently, we have found that neutral (uncharged) organic molecules such as *N*,*N*-dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) mediate allylation of aldehydes[5] and *N*-acylhydrazones[6] with allyltrichlorosilanes. Remarkably, the reactions proceeded without the use of any metal catalyst. These organic molecules coordinate to allyltrichlorosilanes to form hypervalent silicon compounds[7] that react with electrophiles efficiently; thus, we defined these molecules as neutral coordinate-organocatalysts (*NCO*s).[8] Quite recently, we have achieved stereospecific, enantioselective allylation of *N*-acylhydrazones by using chiral sulfoxides as chiral *NCO*s.[9] We have also found that phosphine oxides are effective for the allylation of *N*-acylhydrazones.[10] On the basis of this background, we decided to develop the stereospecific, enantioselective allylation of α-imino ester derivatives.

We selected α-hydrazono esters as α-imino ester surrogates because of their stability compared to the corresponding α-imino esters. Indeed, most α-hydrazono esters are crystalline, easily purified by simple recrystallization, and can be stored for several months at room temperature.[3,11] First, the reaction of α-hydrazono ester **4a** (prepared from ethyl glyoxylate and benzhydrazide) with allyltrichlorosilane (**5a**) was chosen as a model, and several enantiopure catalysts were tested (Table 1). When sulfoxide **1** was used as a chiral catalyst, the reaction proceeded to afford the desired allylated adduct **6a** in 60% yield but with disappointingly low enantioselectivity (23% *ee*; Table 1, entry 1). Although several reaction conditions were examined using **1**, little improvement of the yield and the selectivity was observed. We then decided to search for other chiral catalysts for this reaction. After screening several catalysts, we found that 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl dioxides (**2**, BINAP dioxides) were promising. When 1.0 equivalent of (*S*)-BINAP dioxide (**2**) was used in the reaction between **4a** and **5a**, the reaction proceeded in dichloromethane at −78 °C to give the desired adduct **6a** in 62% yield with 96% *ee* (Table 1, entry 4). Unfortunately, use of smaller amounts of (*S*)-BINAP dioxide gave lower yields and enantioselectivities (Table 1,

Table 1: Optimization of reaction conditions.



4a **5a** **6a**



1 **2**

Entry	NCO	x	Conc. [M]	Yield [%]	*ee* [%]
1	**1**	3.0	0.15	60	23 (*S*)
2	**2**	0.2	0.30	11	56 (*R*)
3	**2**	0.4	0.30	38	69 (*R*)
4	**2**	1.0	0.30	62	96 (*R*)
5	**2**	1.0	0.05	72	95 (*R*)
6	**2**	2.0	0.05	91	98 (*R*)

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[**] This work was partially supported by CREST, SORT, ERATO, the Japan Science Technology Corporation (JST), and a Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Sciences (JSPS). BINAP = 2,2′-Bis(diphenylphosphanyl)-1,1′-binaphthyl.

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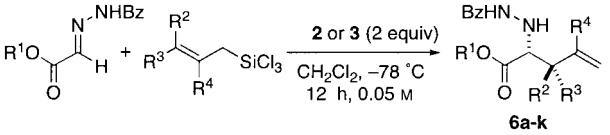
entries 2 and 3). The yield and the selectivity were further improved when two equivalents of **2** were used under lower concentration conditions; thus, the desired adduct **6a** was obtained in 91% yield with 98% *ee* (Table 1, entry 6). After the reaction, **2** was recovered almost quantitatively without loss of optical purity. It is noted that the use of chiral phosphine oxides in asymmetric catalysis has been limited,[12] whereas innumerable usage of BINAP has been reported.[13]

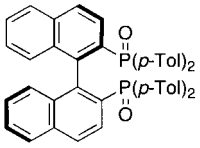
We then examined other α-hydrazono esters and allyltrichlorosilanes, and the results are summarized in Table 2. For

Table 2: Allylation of α-hydrazono esters by using BINAP dioxides.



4a: R^1 = Et
4b: R^1 = *i*Pr
4c: R^1 = *c*Hex
4d: R^1 = Bn

5a: R^2 = H, R^3 = H, R^4 = H
5b: R^2 = H, R^3 = CH_3, R^4 = H
5c: R^2 = CH_3, R^3 = H, R^4 = H
5d: R^2 = H, R^3 = CH_3, R^4 = CH_3
5e: R^2 = CH_3, R^3 = H, R^4 = CH_3
5f: R^2 = H, R^3 = H, R^4 = CH_3
5g: R^2 = H, R^3 = H, R^4 = Ph



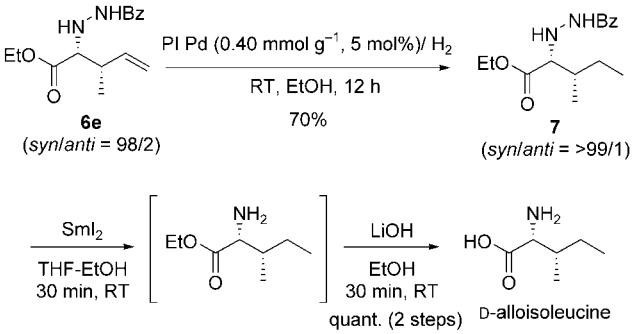
3

Entry	Electrophile	Silane	Yield [%]	*syn*/*anti*	*ee* [%]
1	**4a**	**5a**	91 (**6a**)	–	98 (*R*)
2	**4b**	**5a**	70 (**6b**)	–	97
3	**4c**	**5a**	28 (**6c**)	–	98
4	**4d**	**5a**	12 (**6d**)	–	91
5	**4a**	**5b**	92 (**6e**)	98/2	>99 (2*R*, 3*S*)
6	**4a**	**5c**	96 (**6f**)	<1/>99	96 (2*R*, 3*R*)
7[a]	**4a**	**5d**	80 (**6g**)	98/2	96 (2*S*, 3*R*)
8[a]	**4a**	**5e**	80 (**6h**)	<1/>99	81 (2*S*, 3*S*)
9[b]	**4a**	**5f**	83 (**6i**)	–	94 (*R*)
10[a]	**4a**	**5g**	50 (**6j**)	–	95

[a] Compound **3** was used instead of **2**. Reaction time was 15 h. [b] Reaction time was 6 h.

α-hydrazono esters, larger ester groups gave lower yields, whereas high enantioselectivities were maintained in some cases. For allyltrichlorosilanes, we carefully examined crotylation using (*E*)- and (*Z*)-crotyltrichlorosilanes. It was exciting to find that the reactions proceeded stereospecifically; (*E*)-crotyltrichlorosilane **5b** gave the *syn* adduct **6e** (Table 2, entry 5), whereas the *anti* adduct **6f** was produced from (*Z*)-crotyltrichlorosilane **5c** (Table 2, entry 6).[14] In both cases, yields were high, and excellent diastereo- and enantioselectivities were obtained. When (*E*)- and (*Z*)-allylic trichlorosilanes, **5d** and **5e**, were employed, both *syn* and *anti* adducts were also obtained stereospecifically, although (*R*)-2,2′-bis(di-*p*-tolylphosphanyl)-1,1′-binaphthyl dioxides (**3**, (*R*)-*p*-tol-BINAP dioxides) as an *NCO* gave better results than **2** (Table 2, entries 7 and 8). It is noteworthy that this is the first example of stereospecific, enantioselective allylation of α-imino ester equivalents. Other allylic silanes **5f** and **5g** also worked well to afford the desired adducts with high enantioselectivities (Table 2, entries 9 and 10).

The present allylation was successfully applied to the enantioselective synthesis of D-alloisoleucine, an uncommon α-amino acid observed in biologically important peptides;[15] however, there are several reports on enantioselective synthesis of this molecule.[16] Our synthesis is outlined in Scheme 1. The starting material **6e** is an allylated adduct



Scheme 1. Facile synthesis of D-alloisoleucine.

prepared from **4a** and **5b** (Table 2, entry 5). The olefin moiety of **6e** was reduced by using polymer incarcerated Pd (PI Pd)[17] to give **7** in 70% yield. Successive reductive cleavage of the N–N bond of **7** using SmI_2,[18] followed by ester hydrolysis gave D-alloisoleucine (quantitative yield for two steps). Thus, D-alloisoleucine has been synthesized from α-hydrazono ester **4a** in four steps in an overall yield of 64%. This efficient synthesis demonstrates the utility of the BINAP dioxide-catalyzed enantioselective allylation reaction for amino acid synthesis.

In conclusion, we have found that BINAP dioxides are excellent chiral neutral-coordinate organocatalysts for the enantioselective allylation of α-hydrazono esters using allyltrichlorosilanes. The reactions proceeded stereospecifically; (*E*)-allylic silanes gave *syn* adducts, whereas *anti* adducts were obtained from (*Z*)-allylic silanes. This is the first example of the stereospecific, enantioselective allylation of α-imino ester equivalents. Diastereo- and enantioselectivies obtained in this allylation are very high compared to those reported by previous methods. In addition, the present reaction was successfully applied to the efficient synthesis of D-alloisoleucine. A drawback of this reaction is the use of two equivalents of BINAP dioxides, but the chiral source could be recovered almost quantitatively without loss of optical purity. Further investigations to reduce the amounts of BINAP dioxides are now in progress.

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