Synthetic Methods

Deutsche Ausgabe: DOI: 10.1002/ange.201503928
Internationale Ausgabe: DOI: 10.1002/anie.201503928

Highly *E*-Selective and Enantioselective Michael Addition to Electron-Deficient Internal Alkynes Under Chiral Iminophosphorane Catalysis**

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Abstract: *A highly E-selective and enantioselective conjugate addition of 2-benzyloxythiazol-5(4H)-ones to β-substituted alkynyl N-acyl pyrazoles is achieved under the catalysis of a P-spiro chiral iminophosphorane. Simultaneous control of the newly generated central chirality and olefin geometry is possible with a wide array of the alkynyl Michael acceptors possessing different aromatic and aliphatic β-substituents, as well as the various α-amino acid-derived thiazolone nucleophiles. This protocol provides access to structurally diverse, optically active α-amino acids bearing a geometrically defined trisubstituted olefinic component at the α-position.*

Conjugate addition of enolates (original Michael addition) to electron-deficient alkynes, such as alkynyl carbonyl compounds, offers an extremely powerful tool for incorporating a vinylic component at the α-position to carbonyl functionalities, thus enabling a straightforward entry to a range of β,γ-unsaturated carbonyl compounds.[1,2] Accordingly, stereochemical control involving facial recognition of both the prochiral enolate (enantiocontrol) and the intermediary allenic enolate (olefin geometry control) in this bond-forming process poses an important yet difficult challenge.[3–5] It has been addressed through the development of effective catalytic systems, and recent contributions report high levels of both enantioselectivity and *E*/*Z* selectivity.[6,7] However, most of the existing methods are restricted to reactions with terminal alkynes. Only a few successful examples of stereoselective Michael additions to internal alkynes are known to date, and they specifically deal with dialkyl acetylene dicarboxylates as the acceptor.[8] This methodological deficiency highlights the fact that the full potential of this valuable transformation remains to be realized in terms of simultaneous stereocontrol, general applicability, and synthetic utility. Herein we disclose the first broadly useful, highly *E*-selective, and enantioselective conjugate addition of prochiral enolates to β-substituted alkynyl carbonyl compounds under the catalysis of a chiral iminophosphorane (**1**; Figure 1).[9–13] The vast synthetic potential of this protocol as a means to access various synthetically relevant carbonyl compounds bearing a stereochemically defined, trisubstituted olefinic component at the α-position is demonstrated.

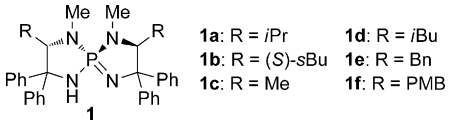
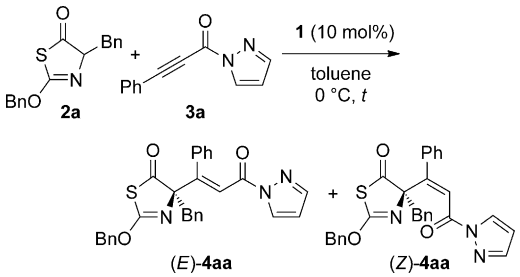


Figure 1. *P*-spiro chiral iminophosphoranes. PMB = *p*-methoxybenzyl.

In consideration of the unique biological properties of α-vinylic amino acids,[14,15] 2-benzyloxythiazol-5(4*H*)-ones (**2**),[16,17] *N*-Cbz amino acid equivalents, were selected as the prochiral enolate precursor. Since initial attempts to promote the conjugate addition of the phenylalanine-derived **2a** (for structure, see Table 1) and methyl 3-phenylpropiolate in the presence of the iminophosphorane **1a** did not result in the formation of the desired adduct to any detectable extent, we

Table 1: Optimization of the catalyst structure.[a]



Entry	R (**1**)	*t* [h]	Yield [%][b]	*E*/*Z*[c]	*ee* [%][d]
1	*i*Pr (**1a**)	12	69	8.3:1	96
2	(*S*)-*s*Bu (**1b**)	10	24	1.2:1	63
3	Me (**1c**)	10	73	6.3:1	95
4	*i*Bu (**1d**)	10	66	5.9:1	91
5	Bn (**1e**)	11	72	>20:1	98
6	PMB (**1f**)	10	91	>20:1	98

[a] Reactions were performed with 0.11 mmol of **2a** and 0.1 mmol of **3a** in toluene (1.0 mL) in the presence of **1** (10 mol%) at 0°C. [b] Yield of the isolated *E*/*Z* mixture. [c] Determined by ^{1}H NMR (400 MHz) analysis of the crude reaction mixture. [d] Absolute configuration of (*E*)-**4aa** was assigned by analogy to that of (*E*)-**4ag**. The *ee* values of (*E*)-**4aa** were determined by HPLC analysis using a chiral stationary phase (Daicel CHIRALPAK IE-3; *n*-hexane/2-propanol = 19:1 as eluent).

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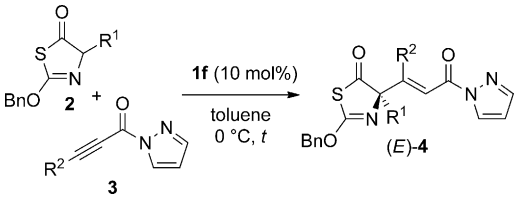
[**] Financial support was provided by CREST-JST, a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT, Program for Leading Graduate Schools "Integrative Graduate Education and Research Program in Green Natural Sciences" in Nagoya University, Grants of JSPS for Scientific Research, and the Asahi Glass Foundation.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201503928.

sought to employ more electrophilic alkynyl carboxylic ester surrogates as the acceptors and focused our attention on the *N*-acyl pyrazoles **3** (Table 1).[18–20] Thus, **2a** was treated with **3a** in the presence of **1a** (10 mol%) in toluene at 0°C. The reaction proceeded smoothly to give the conjugate adduct **4aa** in 69% yield (entry 1). The ^{1}H NMR (400 MHz) analysis of the crude reaction mixture revealed the preferential formation of the *E* isomer (*E*/*Z* = 8.3:1) with an enantiomeric excess of 96%.[21] This promising result encouraged us to examine the effect of the catalyst structure on the reactivity and *E*/*Z* selectivity, thus showing the importance of the alkyl substituents (R) on the diazaphosphacycles in **1**. While both *E*/*Z* selectivity and enantioselectivity were diminished when using iminophosphoranes having saturated alkyl groups (entries 2–4), the use of the benzyl-substituted **1e** delivered an improved *E*/*Z* selectivity and even higher *ee* value (entry 5). Notably, the difficulty encountered in attaining geometrically defined **4aa** in racemic reactions with common achiral organic bases underscores a distinct feature of the present iminophosphorane catalysis.[22] Further investigation allowed identification of **1f**, possessing *para*-methoxybenzyl (PMB) group, as the optimal catalyst in terms of reactivity and selectivity, as essentially stereochemically pure (*E*)-**4aa** was isolated in 91% yield within 10 hours (entry 6).[23]

Table 2: Substrate scope.[a]

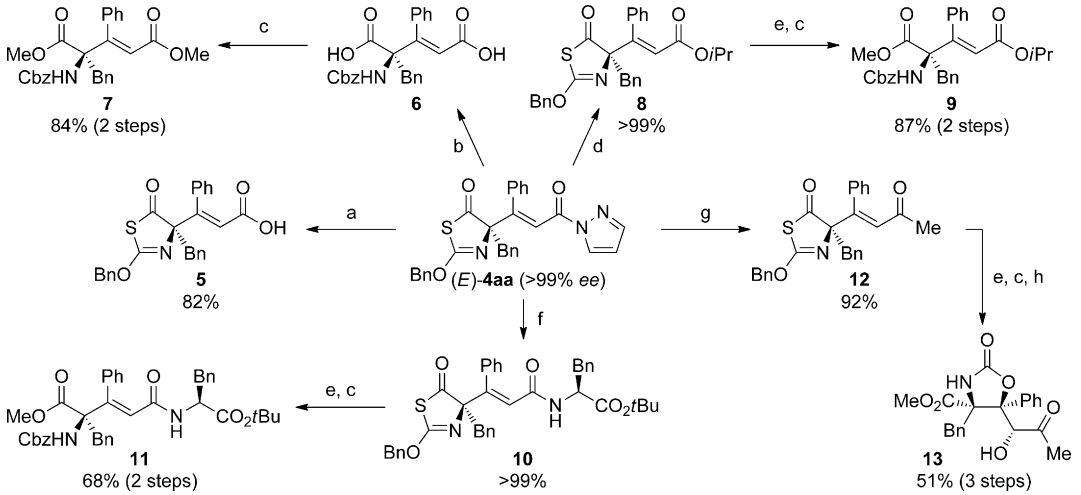


Entry	R^1 (**2**)	R^2 (**3**)	*t* [h]	**4**	Yield [%][b]	*E*/*Z*[c]	*ee* [%][d]
1[e]	Bn (**2a**)	4-$MeOC_6H_4$ (**3b**)	10	**4ab**	85	>20:1	98
2[e]	Bn (**2a**)	4-MeC_6H_4 (**3c**)	10	**4ac**	77	>20:1	98
3	Bn (**2a**)	4-BrC_6H_4 (**3d**)	12	**4ad**	91	>20:1	98
4	Bn (**2a**)	4-ClC_6H_4 (**3e**)	11	**4ae**	92	>20:1	98
5	Bn (**2a**)	3-$MeOC_6H_4$ (**3f**)	10	**4af**	93	>20:1	98
6	Bn (**2a**)	3-BrC_6H_4 (**3g**)	12	**4ag**	91	>20:1	98
7[f]	Bn (**2a**)	2-MeC_6H_4 (**3h**)	18	**4ah**	84	19:1	99
8[f]	Bn (**2a**)	2-FC_6H_4 (**3i**)	10	**4ai**	79[g]	11:1	94
9	Bn (**2a**)	2-naphthyl (**3j**)	10	**4aj**	84	>20:1	98
10	Bn (**2a**)	2-furyl (**3k**)	12	**4ak**	85	>20:1	91
11[f]	Bn (**2a**)	Me (**3l**)	18	**4al**	85[g]	17:1	93
12[f]	Bn (**2a**)	$Me(CH_2)_5$ (**3m**)	18	**4am**	71[g]	16:1	95
13[f]	Bn (**2a**)	$MeOCH_2$ (**3n**)	10	**4an**	83[g]	17:1	94
14	Bn (**2a**)	*i*Bu (**3o**)	12	**4ao**	77[g]	9:1	95
15	Me (**2b**)	Ph (**3a**)	10	**4ba**	96	>20:1	99
16	$MeS(CH_2)_2$ (**2c**)	Ph (**3a**)	10	**4ca**	91	>20:1	98
17	*i*Bu (**2d**)	Ph (**3a**)	10	**4da**	83	>20:1	98
18[h]	Bn (**2a**)	Ph (**3a**)	10	**4aa**	89	>20:1	98

[a] Unless otherwise noted, reactions were conducted with 0.11 mmol of **2** and 0.1 mmol of **3** in toluene (1.0 mL) in the presence of **1f** (10 mol%) at 0°C. [b] Yield of the isolated mixture of *E*/*Z* isomers. [c] Determined by ^{1}H NMR (400 MHz) analysis of the crude reaction mixture. [d] Absolute configuration of (*E*)-**4ag** was determined by X-ray diffraction analysis of its single crystal and that of the products (*E*)-**4** was assigned by analogy. The *ee* values of the major *E* isomer were determined by HPLC using a chiral stationary phase. [e] Used 1.5 equiv of **2a**. [f] Reaction was run at −20°C. [g] Yield of the isolated product (*E*)-**4**. [h] Reaction was performed on a 3.0 mmol scale with 5 mol% of **1f**.

With the information of the catalytic and chiral efficiencies of **1f** in hand, the scope of this new stereoselective conjugate addition protocol was explored. The representative results are summarized in Table 2. With respect to the alkynyl carbonyl acceptors **3**, a variety of aromatic groups having different electronic properties could be used as a terminal substituent without having a detrimental impact on the stereochemical outcome (entries 1–8). However, the steric nature of the *ortho*-substituted aryl units caused slight erosion of the *E*-selectivity, even at a lower reaction temperature (entries 7 and 8). Naphthyl- and furyl-substituted acceptors were also amenable to this conjugate addition system (entries 9 and 10). In addition, this transformation readily tolerated linear aliphatic moieties at the alkyne terminus by adopting mildly cryogenic conditions (entries 11–13). Although comparable enantioselectivity was attained with alkynyl *N*-acyl pyrazoles possessing branched alkyl substituents, such as isobutyl, at the 3-position, the bond formation was slow and accompanied by a decrease in the *E* selectivity (entries 14). As an enolate precursor, an array of thiazol-5(4*H*)-ones **2** bearing different α-side chains of amino acid origin were employed and the corresponding conjugate adducts (*E*)-**4** were obtained with excellent levels of geometrical control and enantiocontrol (entries 15–17).[24] Absolute stereochemistry of the product was unambiguously determined to be *R*,*E* by single-crystal X-ray diffraction analysis of (*E*)-**4ag** (Figure 2).[25] Finally, the scalability of this method was demonstrated in the reaction between **2a** and **3a** with a reduced catalyst loading, thus providing a gram quantity of (*E*)-**4aa** with identical stereoisomeric purity (entry 18).

The salient aspect of this **1f**-catalyzed stereoselective conjugate addition is highlighted by the facile conversion of the product (*E*)-**4**, equipped with two masked acyl units, into structurally diverse α-amino acid derivatives, bearing geometrically defined trisubstituted olefins, without any detectable racemization (Scheme 1). Treatment of stereochemically pure (*E*)-**4aa** (recrystallized) with K_2CO_3 in H_2O/THF effected the selective hydrolysis of the *N*-acyl pyrazole unit to give the carboxylic acid **5**. In contrast, subjecting (*E*)-**4aa** to aqueous lithium hydroperoxide (LiOOH) facilitated the hydrolysis of both reactive sites and simultaneous oxidation of the intermediary formed thiocarbonyl moiety to furnish the *N*-protected amino diacid **6**. This process takes advantage of the latent character of the benzyloxythiazolone as an *N*-Cbz amino acid equivalent and the stereochemical integrity of **6**



Scheme 1. Derivatization. Reaction conditions: a) K_2CO_3, H_2O/THF (1:1), 50 °C; b) LiOH, H_2O_2, H_2O/THF (1:2), RT; c) Me_3SiCHN_2, benzene/MeOH (7:3), RT; d) LiCl, Et_3N, IPA/THF (4:1), RT; e) LiOH, NH_4Cl, H_2O_2, H_2O/THF (1:2), RT; f) L-PheO*t*Bu, HOBt, toluene, 50 °C; g) MeMgI, ether, −78 to −20 °C; h) $TiCl_4$, CH_2Cl_2, RT. Cbz = carboxybenzyl, IPA = isopropyl alcohol, THF = tetrahydrofuran.

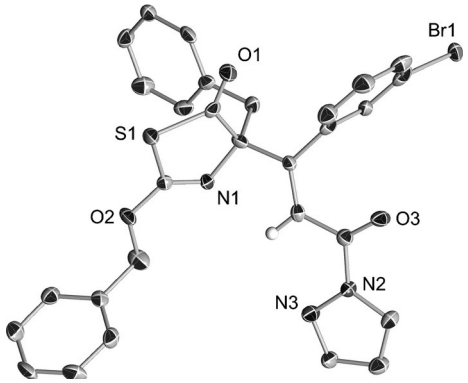


Figure 2. ORTEP diagram of (*E*)-**4ag**. Ellipsoids displayed at 50% probability. Calculated hydrogen atoms, except for that attached to the olefinic carbon atom, are omitted for clarity.

was confirmed by the ^{1}H NMR and HPLC analyses of its methyl ester (**7**). The inherent attribute of *N*-acyl pyrazole as an acylating agent offers an opportunity of readily replacing the pyrazole moiety with various nucleophiles. For instance, (*E*)-**4aa** could be transformed into the ester **8** by displacement with isopropoxide, and to the amide **10** by the coupling with L-phenylalanine *tert*-butyl ester (L-PheO*t*Bu). The resulting intermediates **8** and **10** were further derivatized into the corresponding differently protected, highly functionalized α-vinylic α-amino acids **9** and **11**, respectively, through thiazolone ring-opening under oxidative conditions. Moreover, the reaction with a Grignard reagent enabled the generation of a ketone carbonyl in **12**. It is worthy to emphasize that stereochemical information of the trisubstituted olefinic component can be transmitted to downstream transformations initiated by olefin functionalization. Upon exposure of **12** to LiOOH, diastereoselective epoxidation of the enone component took place in concurrence with the thiazolone cleavage to afford an epoxy ketone, which was subsequently converted into the hydroxy ketone **13** with high stereospecificity by esterification and $TiCl_4$-promoted epoxide ring opening.

In conclusion, we have developed a general, highly *E*-selective and enantioselective conjugate addition of prochiral enolates to electron-deficient internal alkynes by using 2-benzyloxythiazol-5(4*H*)-ones as pronucleophiles and β-substituted alkynyl *N*-acyl pyrazoles as acceptors, under the catalysis of *P*-spiro chiral iminophosphoranes. The synthetic utility of this new methodology has been amply demonstrated through a series of derivatizations of the product, which features two masked acyl units and a stereochemically defined trisubstituted olefinic component, into a wide range of optically active α-vinylic α-amino acid derivatives. Investigations on the mechanistic details of the simultaneous stereocontrol are currently underway.

Keywords: asymmetric catalysis · amino acids · Michael addition · organocatalysis · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 9954–9957
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[21] *E*/*Z* geometry of the major isomer of **4aa** was initially assigned to be *E* by NOESY experiments, where an NOE correlation between the olefinic proton and benzyl moiety was observed. Accuracy of the stereochemistry was eventually confirmed by X-ray diffraction analysis of its analogue (*E*)-**4ag** (see Figure 2). For identifying the geometry of the minor isomer of **4aa**, the major isomer (*E*)-**4aa** was exposed to UV irradiation to initiate *E*/*Z* isomerization for converting (*E*)-**4aa** into the corresponding *Z* isomer.

[22] The results of the reactions with common organic bases as catalysts are as follows: 1,1,3,3-tetramethylguanidine (TMG): 23 h, trace; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU): 23 h, 56% conv., *E*/*Z* = 1:1; 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD): 35 h, 66% conv., *E*/*Z* = 1.1:1; BEMP: 35 h, 34% conv., *E*/*Z* = 1:3.3.

[23] In contrast to our previous report (Ref. [13]), use of a pseudo-diastereomeric iminophosphorane, having opposite *P*-spiro chirality, as a catalyst did not cause a reversal of *E*/*Z* selectivity.

[24] The reaction of 4-phenyl 2-benzyloxythiazol-5(4*H*)-one (**2**, R^1 = Ph) with **3a** under the standard reaction conditions did not produce the desired product, probably because of the insufficient nucleophilicity of the enolate derived from this thiazolone.

[25] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1055552. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Received: April 29, 2015
Published online: July 1, 2015

