Asymmetric Synthesis

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Highly *Z*-Selective Asymmetric Conjugate Addition of Alkynones with Pyrazol-5-ones Promoted by *N*,*N*′-Dioxide–Metal Complexes**

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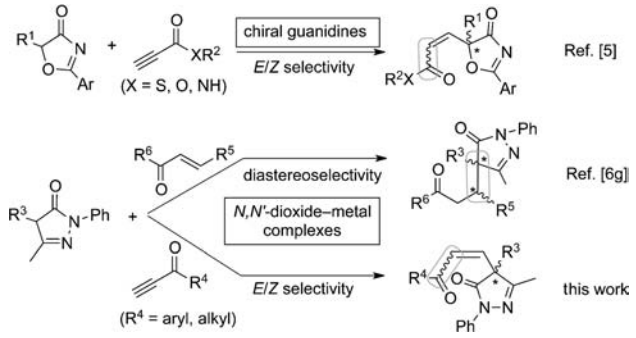
The catalytic enantioselective conjugate addition of carbon nucleophiles to alkynyl carbonyl compounds is an efficient way to construct versatile and useful building blocks because the newly formed C=C bond can be further functionalized.[1] However, in contrast to extensive and fruitful studies on asymmetric 1,4-addition reactions of electron-deficient alkenes, investigations of conjugate additions of electron-deficient alkynes are still limited (Scheme 1).[2] The difficulty in controlling both *E*/*Z* selectivity[3] and enantioselectivity is



Scheme 1. Conjugate addition of carbon nucleophiles to alkenes and alkynyl carbonyl compounds.

probably the reason for the limited amount of studies. In general, the predominant product is the thermodynamically stable *E* isomer, the unstable *Z* isomer can be transformed into the *E* isomer by isomerization after the 1,4-addition reaction.[2a,d,4] For example, β-dicarbonyl compounds and α-substituted α-cyanoacetate have both been successfully used in the asymmetric conjugate additions of alkynes and furnished preferably the *E* isomers.[2] Even now, there is only one example of a highly *Z*-selective asymmetric 1,4-addition of 5*H*-oxazol-4-ones to alkynyl carbonyl compounds, reported by Sugimura and co-workers who used chiral guanidine catalysts.[5] The highly *Z*-selective control in the asymmetric 1,4-addition of acetylenic ketone has not been achieved yet.

Recently, we demonstrated that *N*,*N*′-dioxide–metal complexes are efficient catalysts for a number of enantioselective reactions.[6] During the course of developing new asymmetric transformations, the asymmetric 1,4-addition reaction of pyrazol-5-ones to alkynones is therefore desirable. Herein, we present our intensive study on the asymmetric 1,4-addition of 4-substituted pyrazol-5-ones to alkynones by using *N*,*N*′-dioxide–metal complexes, thus providing the thermodynamically unstable *Z* isomers in high enantiomeric and geometric control. In addition, the reaction afforded enantiomerically enriched pyrazolone isomers with vinyl-substituted quaternary stereocenters.[7]

Initially, we examined the *N*,*N*′-dioxide **L1**, which was coordinated in situ with various rare-metal salts to catalyze the conjugate addition of 4-benzyl-1*H*-pyrazol-5-one (**1a**) to 1-phenylprop-2-yn-1-one (**2a**) in CH_2Cl_2 at 0°C (Table 1). $Gd(OTf)_3$ and $Ho(OTf)_3$ promoted the reaction smoothly and gave the thermodynamically stable *E* isomer (**3a**) in insufficient geometric control and moderate enantioselectivity for *Z*/*E* isomers (Table 1, entries 1 and 2). With the assistance of 4 Å molecular sieves and use of **L1**–$Ho(OTf)_3$ as catalyst, the yield of the *Z* isomer exceeded that of *E* isomer, and the *ee* value of the *Z* isomer could be improved to 91% (Table 1, entry 3).[8] More interestingly, **L1**–$Sc(OTf)_3$ catalyst afforded the *Z* isomer **3a** as the major product, albeit with low yield (Table 1, entry 4). The addition of 4 Å molecular sieves increased the yield of product **3a** greatly (Table 1, entry 5). The *Z* isomer (**3a**) was stable at room temperature, and the absolute configuration of the predominated enantiomer (Table 1, entry 3) was determined to be (*Z*,*S*) by X-ray crystallography (see the Supporting Information for details).[9]

Encouraged by these results, a series of *N*,*N*′-dioxides were synthesized and combined with scandium triflate to enhance the *Z* selectivity and enantioselectivity of the reaction (Table 1, entries 5–8). The steric effect of the amide moiety of the *N*,*N*′-dioxide ligands played a crucial role on the enantioselectivity of the reaction (Table 1). The aniline derived *N*,*N*′-dioxide **L2** dramatically reduced the enantioselectivity to 19% *ee* (Table 1, entry 6 versus entry 5). It is noteworthy that under similar reaction conditions, aliphatic amine derived *N*,*N*′-dioxide **L3** showed an notable reversed enantioinduction and gave (*Z*,*R*)-**3a** as the major product (>95:5 *Z*/*E*, 86% *ee*, Table 1, entry 7 versus entry 5). L-Proline-derived *N*,*N*′-dioxide **L4** proved to be the most promising catalyst of those tested with an amino acid backbone (Table 1, entry 8 versus entry 7). The addition

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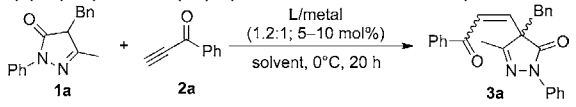
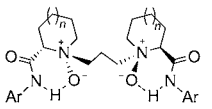
Table 1: Optimization of 1,4-addition of 4-benzyl-pyrazol-5-one (**1a**) to 1-phenylprop-2-yn-1-one (**2a**) by *N*,*N*′-dioxide–metal complexes.[a]





L1: Ar = 2,6-diethylphenyl, *n* = 1
L2: Ar = phenyl, *n* = 1
L3: Ar = 1-adamantyl, *n* = 1
L4: Ar = 1-adamantyl, *n* = 0

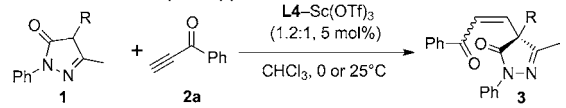
Entry	Ligand	Metal	Solvent	Yield [%][b]	*Z*/*E* ratio[c]	*ee* [%][d]
1[e]	**L1**	$Gd(OTf)_3$	CH_2Cl_2	89	33/67	78 (*S*)
2[e]	**L1**	$Ho(OTf)_3$	CH_2Cl_2	87	15/85	67 (*S*)
3	**L1**	$Ho(OTf)_3$	CH_2Cl_2	92	84/16	91 (*S*)[f]
4[e]	**L1**	$Sc(OTf)_3$	CH_2Cl_2	30	90/10	52 (*S*)
5	**L1**	$Sc(OTf)_3$	CH_2Cl_2	62	90/10	52 (*S*)
6	**L2**	$Sc(OTf)_3$	CH_2Cl_2	35	80/20	19 (*R*)
7	**L3**	$Sc(OTf)_3$	CH_2Cl_2	85	>95/5	86 (*R*)
8	**L4**	$Sc(OTf)_3$	CH_2Cl_2	96	>95/5	95 (*R*)
9	**L4**	$Sc(OTf)_3$	$CHCl_3$	97	94/6	99 (*R*)
10[g]	**L4**	$Sc(OTf)_3$	$CHCl_3$	97	94/6	97 (*R*)
11[g,h]	**L4**	$Sc(OTf)_3$	$CHCl_3$	97	94/6	97 (*R*)
12[g,i]	**L4**	$Sc(OTf)_3$	$CHCl_3$	98	90/10	99 (*R*)
13[g]	*ent*-**L4**	$Sc(OTf)_3$	$CHCl_3$	96	94/6	96 (*S*)
14[g–k]	**L4**	$Sc(OTf)_3$	$CHCl_3$	95	<5/95	98 (*R*)

[a] Unless otherwise noted, reactions were carried out with ligand (12 mol%), metal (10 mol%), **1a** (0.1 mmol), **2a** (0.11 mmol), and molecular sieves (4 Å, 30 mg) in solvent (1.0 mL) at 0°C for 20 hours. [b] Yield of isolated *Z*/*E*-**3a**. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] *ee* value of the *Z* isomers determined by chiral HPLC analysis. [e] Without 4 Å molecular sieves. [f] The absolute configuration was determined by X-ray analysis. [g] 5 mol% of catalyst, 36 hours. [h] The catalyst was pre-prepared in the presence of 4 Å molecular sieves. [i] At 25°C for 6 hours. [j] After the 1,4-addition, Ph_2MeP (0.3 equiv) was added for the isomerization (24 h). [k] *ee* of the *E* isomer. Tf = trifluoromethanesulfonyl.

product was obtained in up to 95/5 *Z*/*E* ratio and 95% *ee* (Table 1, entry 8). A screening of solvents (Table 1, entries 8 and 9) showed that an *ee* value of 99% could be obtained in $CHCl_3$ with a little decrease in the *Z*/*E* selectivity (Table 1, entry 9). Notably, when the catalyst loading was lowered to 5 mol%, the reaction performed well with good results (Table 1, entry 10). Furthermore, the yield, *Z*/*E* selectivity, and enantioselectivity were basically maintained by employing the catalyst that was prepared before the reaction, thus facilitating the experimental procedure (Table 1, entry 11). Excellent enantioselectivity was afforded at 25°C, although the *Z*/*E* ratio was somewhat reduced (Table 1, entry 12). The opposite enantioselectivity was further confirmed by using the alternative catalyst of D-proline-derived ligand **L4** (Table 1, entry 13). In addition, as reported by Shibasaki and co-workers, Ph_2MeP could be added to the *Z*/*E*-mixed adduct **3a** for isomerization, thus affording exclusively the *E* isomer with 98% *ee* (Table 1, entry 14).[2d] This is an efficient and economical method to afford both enantioenriched products with complementary geometric configuration. Thus, the optimized reaction conditions for the 1,4-addition reaction of 4-substituted pyrazol-5-ones to alkynones included the reaction in $CHCl_3$ and use of 5 mol% of *N*,*N*′-dioxide **L4**–Sc^{III} complex (Table 1, entry 11).

With the established optimized reaction conditions, the substrate scope of the 1,4-addition reaction of various pyrazolones and alkynones was examined next. First, a series of pyrazolone derivatives bearing a benzyl group at the C4 position were investigated (Table 2). The study showed that the electronic nature and the position of the substituents on the aromatic ring of the R group had no

Table 2: Substrate scope of pyrazol-5-ones.[a]



Entry	R	*t* [h]	Yield [%][b]	*Z*/*E*[c]	*ee* [%][d]
1	Bn	36	97 (**3a**)	94/6	97 (*R*)
2[e]	2-$MeC_6H_4CH_2$	7	96 (**3b**)	92/8	97 (*R*)
3	3-$MeC_6H_4CH_2$	36	93 (**3c**)	94/6	97 (*R*)
4	4-$MeC_6H_4CH_2$	40	91 (**3d**)	93/7	97 (*R*)
5	2-$MeOC_6H_4CH_2$	36	93 (**3e**)	94/6	97 (*R*)
6	3-$MeOC_6H_4CH_2$	36	92 (**3f**)	94/6	98 (*R*)
7	4-$MeOC_6H_4CH_2$	36	93 (**3g**)	94/6	98 (*R*)
8[e]	2-$ClC_6H_4CH_2$	6	94 (**3h**)	91/9	95 (*R*)
9	3-$ClC_6H_4CH_2$	30	95 (**3i**)	93/7	97 (*R*)
10	4-$ClC_6H_4CH_2$	30	93 (**3j**)	90/10	98 (*R*)
11	4-$BrC_6H_4CH_2$	30	96 (**3k**)	89/11	99 (*R*)
12[e]	2,4-$Cl_2C_6H_3CH_2$	6	97 (**3l**)	88/12	98 (*R*)
13	3,4-$Cl_2C_6H_3CH_2$	24	94 (**3m**)	92/8	97 (*R*)
14[e]	2-furanylmethyl	6	93 (**3n**)	86/14	98 (*R*)
15	2-thienylmethyl	30	97 (**3o**)	92/8	99 (*R*)
16[e]	1-naphthylmethyl	10	95 (**3p**)	89/11	99 (*R*)
17	2-naphthylmethyl	40	92 (**3q**)	93/7	95 (*R*)
18[e]	Me	10	90 (**3r**)	86/14	92 (*R*)
19	Et	36	91 (**3s**)	87/13	99 (*R*)
20	n-propyl	36	90 (**3t**)	89/11	99 (*R*)
21[e]	cyclohexylmethyl	10	96 (**3u**)	88/12	99 (*R*)

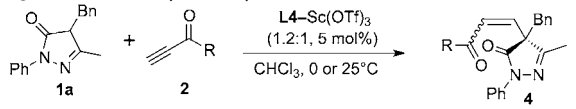
[a] Unless otherwise noted, reactions were carried out under the optimized reaction conditions at 0°C. [b] Yield of isolated *Z*/*E*-**3**. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] *ee* of the *Z* isomer determined by chiral HPLC analysis. [e] At 25°C. Bn = benzyl.

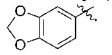
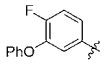
influence on the enantioselectivity, but a slight influence on the *Z*/*E* selectivity and the reaction rate (Table 2, entries 1–13). Relatively lower *Z*/*E* ratios were obtained with halogen substituents at *ortho* or *para* positions (Table 2, entries 8–13 versus entries 1–7). In addition, substrates bearing a condensed ring or heteroaromatic ring at the R substituent were also suitable substrates for the reaction and afforded the corresponding products **3n**–**q** with excellent enantioselectivities and uniformly high *Z*/*E* selectivities (86:14–93:7 *Z*/*E*, 95–99% *ee*; Table 2, entries 14–17). It is worth pointing out that the catalyst system was also efficient when the R substituent was a linear alkyl group (Table 2, entries 18–20) or a cyclohexylmethyl group (Table 2, entry 21). The corresponding adducts **3r**–**u** were generated in good yields with 92–99% *ee* and good *Z*/*E* selectivities. A comparison with the Cotton effect in the CD spectra of *Z*-**3a** showed that the absolute configuration of the other *Z*-isomers was *R* (see the Supporting Information for details).

With these results in hand, a wide range of aromatic, aliphatic, and heterocyclic alkynone derivatives were inves-

tigated with 4-benzyl-pyrazol-5-one (**1a**) as the nucleophile (Table 3). To our delight, this catalyst system showed a remarkably broad substrate scope. The desired adducts were obtained in high yields (85–95%) and good geometric

Table 3: Substrate scope of alkynones.[a]



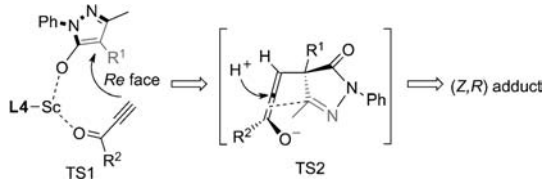
Entry	R	*t* [h]	Yield [%][b]	*Z*/*E*[c]	*ee* [%][d]
1[e]	2-MeC_6H_4	12	95 (**4a**)	91/9	99 (*R*)
2	3-MeC_6H_4	36	93 (**4b**)	93/7	97 (*R*)
3	4-MeC_6H_4	48	90 (**4c**)	95/5	98 (*R*)
4	2-FC_6H_4	24	93 (**4d**)	91/9	96 (*R*)
5	4-FC_6H_4	36	93 (**4e**)	89/11	96 (*R*)
6	4-ClC_6H_4	30	92 (**4f**)	94/6	96 (*R*)
7	4-BrC_6H_4	36	90 (**4g**)	93/7	96 (*R*)
8[e]	4-$CF_3C_6H_4$	3	93 (**4h**)	84/16	97 (*R*)
9[e]	3-$CF_3C_6H_4$	3	94 (**4i**)	78/22	95 (*R*)
10[e]	4-MeOC_6H_4	18	93 (**4j**)	>95/5	98 (*R*)
11[e]		30	91 (**4k**)	>95/5	99 (*R*)
12		48	92 (**4l**)	88/12	91 (*R*)
13	2-naphthyl	36	91 (**4m**)	>95/5	98 (*R*)
14	2-thienyl	30	92 (**4n**)	89/11	96 (*R*)
15[e]	cyclohexyl	18	90 (**4o**)	88/12	97 (*R*)
16[e]	*n*-pentyl	30	85 (**4p**)	92/8	98 (*R*)
17[e,f]	2-MeC_6H_4	24	96 (**4a**)	90/10	99 (*R*)

[a–e] See the corresponding footnotes in Table 2. [f] The reaction was carried out on a gram scale in $CHCl_3$ (30 mL) at 25 °C.

and enantiomeric control (78/22 to >95:5 *Z*/*E*, 91 to 99% *ee*). The electronic properties of the substituent on the aromatic ring of the alkynone had no obvious effect on the enantioselectivity of the reaction (Table 3, entries 1–10), whereas the *Z*/*E* selectivities were reduced and a shorter reaction time was needed when substrates that contained electron-withdrawing substituents were used (Table 3, entries 8 and 9 versus entries 10 and 11). Remarkably, alkynones with two substituents on the aromatic ring, which were rarely investigated previously, underwent the reaction smoothly with excellent results (Table 3, entries 11 and 12). The alkynones bearing condensed-ring or heteroaryl units also proved tolerable with respect to enantioselectivity and *Z*/*E* selectivity of the reaction (Table 3, entries 13 and 14). Notably, the alkyl-substituted alkynones gave predominantly *Z* adducts **4o** (90% yield, 97% *ee*) and **4p** (85% yield, 98% *ee*; Table 3, entries 15 and 16, respectively).

Furthermore, when the reaction of pyrazolone **2a** was carried out on a gram scale with 5 mol% of the chiral scandium complex, good results with 96% yield (1.488 g), 90:10 *Z*/*E*, and 99% *ee* were still obtained (Table 3, entry 17).

In order to elucidate the reaction process, some control experiments were performed. The HRMS analysis of the catalyst and an observed straight linear effect[10] indicate that the monomeric catalyst might be the main catalytically active species (see the Supporting Information for details). We propose that the carbonyl group of the 4-substituted pyrazol-5-one **1** would coordinate to the active **L4***–Sc^{III} complex to form an enolate intermediate. Meanwhile, alkynone, which is structurally similar to enone, coordinated to the central metal at the favorable position (Scheme 2). Subsequently, the electrophilic attack of alkynone to the enolate (**TS 1**) would afford the corresponding adduct with excellent enantioselectivity.



Scheme 2. Proposed catalytic model. TS = transition state.

According to the reported *Z*-selective conjugate addition of carbon nucleophiles to acetylenic esters by using basic catalysts,[5,11] the nature of the pronucleophile might play a crucial role on the *Z*/*E* selectivity. The electron-donating R group on electrophile **2** had a positive effect on the *Z*/*E* selectivity (Table 3). Therefore, we postulate a similar intermediate to that of Sugimura and co-workers[5] to rationalize the sense of geometric induction. One side of the dienolate is shielded by the pyrazoline ring because of the interaction between electron-enriched π orbital of dienolate and electron-deficient carbon atom at the 3 position of the pyrazoline ring.[12] The protonation process occurs from the other side to afford the thermodynamically unstable *Z* isomer.

In summary, we have successfully developed the highly *Z*-selective asymmetric 1,4-addition reaction of 4-substituted pyrazolones to alkynones. The reactions were catalyzed by an *N*,*N*′-dioxide–scandium(III) complex to give the optically active 4-alkenyl-pyrazol-5-ones in high geometric control (*Z*/*E* up to 95/5), high yields (up to 97%), and excellent enantioselectivities (up to 99% *ee*). In particular, the procedure tolerates a relatively wide range of substrates, and excellent results can be obtained on a gram scale. The thermodynamically stable *E* adducts could also be generated through an isomerization procedure. Given the acceptable catalyst loading, mild reaction conditions, simple operation, and the fact that diverse functional groups in the adducts are ready for further conversion, this strategy may find a promising application in organic synthesis. Further studies are underway to investigate the enantiomeric discrimination and the synthetic utility of the α-alkenylation products.

Experimental Section

Typical experimental procedure for 1,4-addition reaction of 4-substituted pyrazol-5-ones to alkynones: The prepared chiral catalyst (5 mol%; see Supporting Information) and 4-benzyl-pyrazol-5-one (**1a**, 26.4 mg, 0.10 mmol) were stirred in $CHCl_3$ (0.9 mL) under nitrogen at room temperature for 10 min. Alkynone (**2a**, 14.3 mg, 0.11 mmol in 0.1 mL $CHCl_3$) was added at 0 °C. The mixture was stirred at 0 °C for 36 h. The *Z*/*E* ratio (94/6) was determined by ^{1}H NMR analysis of the crude mixture. Separation by column

chromatography on silica gel with petroleum ether/ethyl acetate (12:1→4:1) afforded the desired product *Z*/*E*-**3a** in 97% yield with 97% *ee* of *Z*-isomer.

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Keywords: 1,4-addition · alkynones · asymmetric catalysis · scandium · *Z* selectivity

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