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Enantioselective synthesis of 1,2,4-triazolines by chiral iron(II)-complex catalyzed cyclization of α-isocyano esters and azodicarboxylates†

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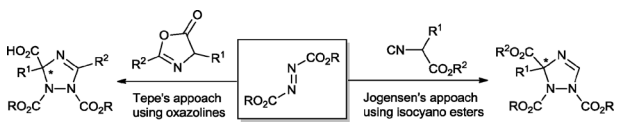
Enantioselective cyclization of α-isocyano esters with azodicarboxylates catalyzed by Fe^{II}–*N*,*N*′-dioxide complexes has been developed. Under mild conditions, a variety of 1,2,4-triazoline derivatives was obtained in high yields and enantioselectivities.

The development of new enantioselective methods for the formation of heterocycles containing a quaternary stereocenter is of importance in pharmaceutical industry, because they exhibit interesting biological activities.[1] The 1,2,4-triazoline core, which belongs to an underutilized class of heterocycles, attracted considerable attention recently.[2] The Tepe[2] group developed a convenient method for the synthesis of 1,2,4-triazolines using oxazolones and azodicarboxylates (Scheme 1). The isocyano ester is an indispensable reagent for the construction of heterocycles.[3,4] 1,2,4-Triazolines with a quaternary C-3 carbon could be accessed by a hydrazination/cyclization cascade of α-isocyano esters and azodicarboxylates reported by the Jørgensen group.[5] The first attempt at synthesizing optically enriched products was by employing a cinchonine-derived-catalyst under phase-transfer conditions (5 equiv. of K_3PO_4 in toluene). Excellent yield but moderate enantioselectivity (up to 60% ee) were obtained. The asymmetric version of the construction of 1,2,4-trizaolines is still in high demand. To minimize the undesired byproduct which results from the versatile reactivity of isocyano esters and to achieve excellent stereocontrol simultaneously are the primary objectives.



Scheme 1 Synthesis of 1,2,4-triazoline.

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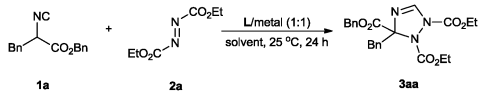
The environmentally benign biometals in organic synthesis such as zinc, iron, and copper have drawn much attention in recent years. Particularly, iron, as one of the most abundant elements on the earth, is nontoxic, inexpensive, readily available, and consequently becomes an ideal candidate.[6] Iron salts were demonstrated to be efficient for many organic processes. However, it is relatively underrepresented compared to other transition metals in the field of asymmetric catalysis.[7] In our continuous effort for developing chiral *N*,*N*′-dioxide ligands promoted asymmetric reactions,[8] we take full advantage of rare earth metal complex catalysts. Herein, we explore the cyclization of α-isocyano esters with azodicarboxylates catalyzed by a chiral *N*,*N*′-dioxide–$Fe(acac)_2$ complex under mild conditions.

Initially, isocyano ester **1a** prepared from phenylalanine by formylation/dehydration protocols and azodicarboxylate **2a** (DEAD) were selected as the model reactants. Chiral Lewis acid catalysts prepared *in situ* from metal salts and *N*,*N*′-dioxide **L1** were used to obtain 1,2,4-triazoline **3aa**. As shown in Table 1, $Fe(acac)_2$ gave the best results among the same periodic metal complexes, such as Sc(III), Co(II), Ni(II), and Zn(II), providing the product in 81% yield with 33% ee (Table 1, entries 1–5). $Fe(acac)_3$ afforded comparable enantioselectivity, excellent conversion but lower yield (Table 1, entry 6). The counterion of iron(II) also greatly affected the reactivity, and $Fe(BF_4)_2$ did not catalyze the reaction at all, clearly indicating that the Lewis acidity of the metal plays an important role in the reaction (Table 1, entries 7 and 8). Encouraged by the results, we investigated the outcome of chiral *N*,*N*′-dioxide ligands with varied amide or amino acid subunits (Fig. 1, **L2–L6**) forming complexes *in situ* with $Fe(acac)_2$ (Table 1, entries 9–13). The chiral backbone of the *N*,*N*′-dioxide ligands is sensitive to the enantioselectivity (Table 1, entry 2 *vs.* entry 9).[9] Ligand **L1** derived from (*S*)-pipecolic acid was superior to **L2** derived from L-proline. From the survey of the amide moiety of the ligand, ligands **L4**, **L5** and **L6** containing alkyl amide gave higher enantioselectivity than **L3** with hindered aryl amide structure, although it exhibited excellent stereocontrol in most cases before (Table 1, entry 10 *vs.* entries 11–13). The bulkier 1-adamantanamine derived **L6** complex of $Fe(acac)_2$ emerged as the most promising catalyst (88% yield, 57% ee; Table 1, entry 13).

Table 1 Optimization of the reaction conditions



1a 2a 3aa

Entry[a]	Ligand	Metal	Solvent	Yield[b] (%)	ee[c] (%)
1	**L1**	$Sc(OTf)_3$	THF	0	—
2	**L1**	$Fe(acac)_2$	THF	81	33
3	**L1**	$Co(acac)_2$	THF	44	28
4	**L1**	$Ni(acac)_2$	THF	66	21
5	**L1**	$Zn(OTf)_2$	THF	91	2
6	**L1**	$Fe(acac)_3$	THF	61	31
7	**L1**	$Fe(BF_4)_2$	THF	0	—
8	**L1**	$Fe(OAc)_2$	THF	68	28
9	**L2**	$Fe(acac)_2$	THF	nd[d]	14
10	**L3**	$Fe(acac)_2$	THF	95	27
11	**L4**	$Fe(acac)_2$	THF	85	50
12	**L5**	$Fe(acac)_2$	THF	96	51
13	**L6**	$Fe(acac)_2$	THF	88	57
14	**L6**	$Fe(acac)_2$	MTBE[e]	94	65
15[f]	**L6**	$Fe(acac)_2$	MTBE	70	73
16[f,g]	**L6**	$Fe(acac)_2$	MTBE	99	88
17[f,g,h]	**L6**	$Fe(acac)_2$	MTBE	99	89

[a] Unless otherwise noted, all reactions were carried out with 10 mol% **L**/metal (1 : 1, 10 mol%), **1a** (0.05 mmol), **2a** (0.075 mmol) in 0.5 mL of THF at 25 °C for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Not determined. [e] MTBE = methyl *tert*-butyl ether. [f] 1.0 mL MTBE was used in the reaction. [g] $NaBAr^F_4$ ($NaB[3,5\text{-}(CF_3)_2C_6H_3]_4$, 10 mol%) was used as the additive. [h] The loading of catalyst and additive was 5 mol%.

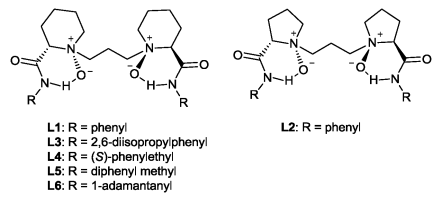
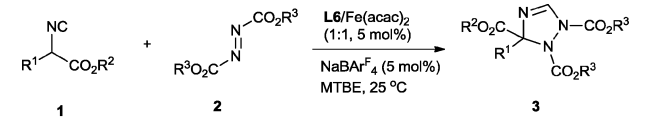


Fig. 1 Chiral ligands used in the study.

To further improve the enantioselectivity, we also undertook some other investigations.[9] Methyl *tert*-butyl ether (MTBE) was found to be superior to THF, generating the desired product **3aa** in 94% yield and 65% ee (Table 1, entry 14). Moreover, reducing the reaction concentration was good for the stereochemical control of the reaction (Table 1, entry 15). Then, we employed several kinds of additives. It seemed that base, salt, phenol and molecular sieves all had a little influence on the enantioselectivity.[9] Fortunately, the treatment of the catalyst with $NaBAr^F_4$ dramatically increased the enantioselectivity of the reaction to 88% ee with excellent yield (Table 1, entry 16). Further optimization of the reaction conditions revealed that by employing 5 mol% of the catalyst, excellent yield and a better ee value would be obtained (99% yield, 89% ee; Table 1, entry 17). After evaluating a variety of conditions, a combination of **L6**–$Fe(acac)_2$–$NaBAr^F_4$ (1 : 1 : 1, 5 mol%), and MTBE as solvent at 25 °C were found to be optimal.

Under the optimized conditions, the substrate scope of isocyano esters and azodicarboxylates was examined. As shown in Table 2, isocyano benzyl esters prepared from various amino acids (R^2 = Bn) were employed in the reaction (Table 2, entries 1–7). When the alkyl substituent (R^1) ranged in size from methyl to iso-butyl group, the corresponding products **3da**, **3ea**, **3fa** gave

Table 2 Substrate scope for the catalytic asymmetric cyclization of isocyano esters with azodicarboxylates[a]



1 2 3

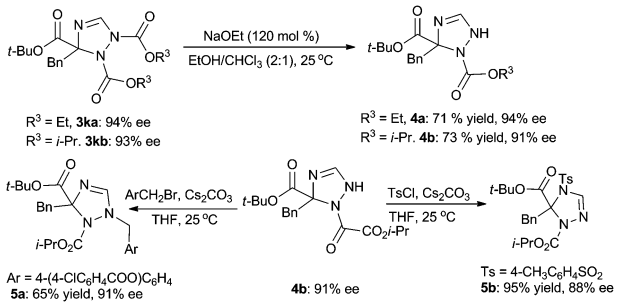
2a: R^3 = Et **2b**: R^3 = *i*-Pr
2c: R^3 = *t*-Bu **2d**: R^3 = Bn

Entry	R^1	R^2	2	Yield[b] (%)	ee[c] (%)
1	Me	Bn (**1d**)	**2a**	86 (**3da**)	82
2[d]	i-Pr	Bn (**1e**)	**2a**	91 (**3ea**)	89
3	i-Bu	Bn (**1f**)	**2a**	91 (**3fa**)	88
4[d]	(*S*)-*sec*-Bu	Bn (**1g**)	**2a**	83 (**3ga**)	80
5	$CbzCH_2$	Bn (**1h**)	**2a**	91 (**3ha**)	83
6	$CbzCH_2CH_2$	Bn (**1i**)	**2a**	98 (**3ia**)	83
7	*o*-$MeOC_6H_4CH_2$	Bn (**1j**)	**2a**	82 (**3ja**)	81
8	Bn	Me (**1b**)	**2a**	88 (**3ba**)	80
9	Bn	Et (**1c**)	**2a**	80 (**3ca**)	81
10	Bn	Bn (**1a**)	**2a**	97 (**3aa**)	89
11[d]	Bn	*t*-Bu (**1k**)	**2a**	91 (**3ka**)	94
12[e]	Bn	*t*-Bu (**1k**)	**2b**	86 (**3kb**)	93
13[e]	Bn	Bn (**1a**)	**2b**	87 (**3ab**)	87
14[e]	Bn	Bn (**1a**)	**2c**	72 (**3ac**)	81
15[e]	Bn	Bn (**1a**)	**2d**	94 (**3ad**)	84

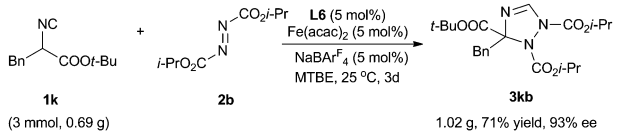
[a] Unless otherwise noted, all reactions were carried out with 5 mol% **L6**/$Fe(acac)_2$ (1 : 1), $NaBAr^F_4$ (5 mol%), **1** (0.1 mmol), **2** (0.15 mmol) in MTBE (2.0 mL) at 25 °C for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 10 mol% of catalyst and additive was used in 1.0 mL of MTBE. [e] 0.2 mmol of **2** was used in the reaction.

slightly improved ee values and yields (Table 2, entries 1–3). However, switching R^1 to *sec*-butyl group diminished the reactivity and ee value a little, which probably could be attributed to the steric hindrance of the branch (81% yield, 80% ee; Table 2, entry 4). Also when cbz containing isocyano esters **1h** and **1i** were used as the starting materials, excellent yields and good enantioselectivities were obtained (Table 2, entries 5 and 6). Moreover, the reaction with isocyano ester **1j** substituted by an *o*-methoxy benzyl group also proceeded well with **2a** to give the desired product **3ja** in excellent yield and good ee value (82% yield, 81% ee; Table 2, entry 6). Furthermore α-isocyano esters with different ester groups (R^2 = Me, Et, *t*-Bu) were also examined (Table 2, entries 8–11). The ester groups had a notable effect on the enantioselectivity and yield of the reaction. Methyl and ethyl group substituted isocyano esters **1b** and **1c** afforded the 1,2,4-trizaoline **3ba**, **3ca** in similar results (Table 2, entry 8 *vs.* entry 9). When the benzyl group was replaced by a bulkier *tert*-butyl group, dramatically increased enantioselectivities were achieved with excellent yields (up to 94% ee; Table 2, entries 11 and 12). In addition, the steric effect of the azodicarboxylate was tested for the asymmetric cyclization of isocyano ester **1a**. The ester groups apparently had a little effect on the enantioselectivity (81–87% ee) of the reaction. DIAD **2b** and DTBAD **2c** were all tolerable, but the yield and enantioselectivity decreased with the increased steric bulk (Table 2, entry 13 *vs.* entry 14). Moreover, the more electrophilic DBAD **2d** remained highly reactive toward the nucleophilic addition (Table 2, entry 15). The reaction behaviour is opposite to the outcomes of DBU-promoted racemic synthesis in the previous study.[5]

The cyclization reaction provided an efficient approach for the synthesis of enantiomerically enriched 1,2,4-triazoline core



Scheme 2 Synthesis of chiral 1,2,4-triazoline derivatives.



Scheme 3 The synthetic utility of this catalyst system.

containing products. To highlight the synthetic potential of the 1,2,4-triazolines **3**, structural elaboration of the heterocycle was carried out and presented in Scheme 2. When treated with 120 mol% of NaOEt in $CHCl_3$–EtOH at 25 °C, both **3ka** and **3kb** were mono-deprotected to provide heterocycles **4a** and **4b** in good yields and excellent ee values. The resulting product **4b**, which contains an active hydrogen, then could be transformed into *N*-benzyl protected **5a** (65% yield, 91% ee) and *N*-Ts protected **5b** (95% yield, 91% ee), respectively.[5]

Gram-scale reaction was also evaluated, and cyclization between isocyano ester **1k** and DIAD **2b** was performed on a 3 mmol scale with 5 mol% of $Fe(acac)_2$/**L6** at 25 °C. As shown in Scheme 3, the desired product **3kb** was obtained with 71% yield and 93% ee.

In summary, we have developed a highly enantioselective cyclization of α-isocyano esters and azodicarboxylates catalyzed by a *N*,*N*′-dioxide/$Fe(acac)_2$ complex. The excellent yields (up to 98%), good enantioselectivities (up to 94% ee), broad substrate scope, mild reaction conditions, and operational simplicity provided a potential method for the asymmetric synthesis of 1,2,4-triazoline derivatives. Further investigations of the *N*,*N*′-dioxide–metal complexes system in other reactions are ongoing.

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9 For more investigations of ligands, solvents, additives details see ESI†.