Asymmetric Synthesis

DOI: 10.1002/anie.201008256

Highly Enantioselective Michael Addition of Pyrazolin-5-ones Catalyzed by Chiral Metal/*N*,*N*′-Dioxide Complexes: Metal-Directed Switch in Enantioselectivity**

*Zhen Wang, Zhigang Yang, Donghui Chen, Xiaohua Liu, Lili Lin, and Xiaoming Feng**

Control of the absolute configuration of newly created stereocenters is of special interest and is still a challenging problem in asymmetric catalysis.[1] Generally, a switch in enantioselectivity is most obviously achieved through the use of enantiomeric ligands. However, the two enantiomers of a chiral ligand are not always readily available or economically feasible to synthesize. Alternatively, the enantioselectivity can also be switched when using the same metal in the presence of ligands that are from the same chiral source but contain modified subunits.[2] The development of new and effective catalytic asymmetric methods to induce a switch in the preferred enantioselectivity of a reaction when using the same chiral ligand is an interesting and demanding challenge. In fact, several metal-based systems, in which the metal and reaction conditions (solvent, pressure, and additive) were tuned, have been developed for this enantiodivergent synthesis.[3] In these systems the unique characteristics of the metal ions, such as the atomic radius and their electronic properties, altered their coordination pattern even with the same chiral ligand. This behavior suggests the existence of different transition states that lead to the switch in enantioselectivity. Pyrazolone derivatives, an important class of five-membered-ring lactams, have exhibited a variety of applications as pharmaceutical candidates and biologically important structural components.[4] The development of asymmetric methods to access pyrazolone enantiomers with the construction of contiguous quaternary and tertiary stereocenters is therefore of considerable interest.[5] To date, there is only one example of the organocatalytic diastereo- and enantioselective Michael addition of 4-substituted-pyrazolin-5-ones to nitroolefins.[4l] We report herein a highly enantioselective Michael addition of 4-substitituted-5-pyrazolones to 1,4-dicarbonyl but-2-enes,[6] using the same ligand with either $Sc(OTf)_3$ or $Y(OTf)_3$ to switch the enantioselectivity.[7]

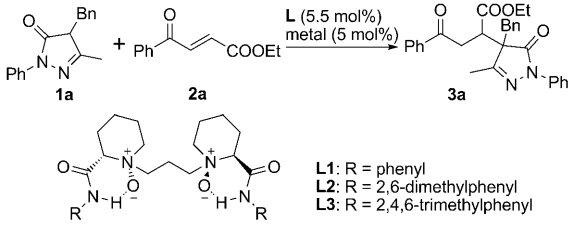
[*] Z. Wang, Z. G. Yang, D. H. Chen, Dr. X. H. Liu, Dr. L. L. Lin, Prof. Dr. X. M. Feng
Key Laboratory of Green Chemistry & Technology
Ministry of Education, College of Chemistry, Sichuan University
Chengdu 610064 (China)
Fax: (+86) 28-8541-8249
E-mail: xmfeng@scu.edu.cn

[**] We acknowledge the National Natural Science Foundation of China (Nos. 20732003 and 21021001), the PCSIRT (No. IRT0846), and the National Basic Research Program of China (973 Program: No. 2011CB808600) for financial support. We also thank the Sichuan University Analytical & Testing Center for NMR analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201008256.

We initially investigated the reaction of 4-benzyl-5-pyrazolone (**1a**) with ethyl (*E*)-4-oxo-4-phenylbutenoate (**2a**) in EtOH at 30 °C catalyzed by scandium(III)/*N*,*N*′-dioxide complexes, which contain ligands that are derived from (*S*)-pipecolic acid (Table 1, entries 1–5). The reaction proceeded smoothly to afford the desired adducts with 2.3:1 d.r. and 75% *ee* (Table 1, entry 1). The *N*,*N*′-dioxides that contained a methyl group at the *ortho* position on the aniline ring exhibited a positive effect on both the diastereoselectivity and enantioselectivity (Table 1, entries 1–3). The yield could be improved to 95% by adding molecular sieves (4 Å; 10 mg). The role of the molecular sieves might be to promote the enolation of pyrazolone and accelerate the

Table 1: Optimization of the Michael addition of 4-benzyl-5-pyrazolone (**1a**) to ethyl (*E*)-4-oxo-4-phenylbutenoate (**2a**) using metal/*N*,*N*′-dioxide complexes.[a]



Entry	Metal	L	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][c,d]
1	$Sc(OTf)_3$	**L1**	EtOH	85	2.3:1	75
2	$Sc(OTf)_3$	**L2**	EtOH	79	3.2:1	83
3	$Sc(OTf)_3$	**L3**	EtOH	80	4.3:1	86
4[e]	$Sc(OTf)_3$	**L3**	EtOH	95	4.6:1	86
5[e,f]	$Sc(OTf)_3$	**L3**	EtOH	80	4.5:1	86
6[g]	$Y(OTf)_3$	**L3**	EtOH	88	>49:1	−65
7[g]	$Y(OTf)_3$	**L3**	THF	86	>49:1	−66
8[g]	$Y(OTf)_3$	**L3**	MeCN	70	>49:1	−81
9[g]	$Y(OTf)_3$	**L3**	CH_2Cl_2	95	>49:1	−96
10[f,g]	$Y(OTf)_3$	**L3**	CH_2Cl_2	73	>49:1	−95
11[g]	$La(OTf)_3$	**L3**	CH_2Cl_2	93	>49:1	−90
12[g]	$Sm(OTf)_3$	**L3**	CH_2Cl_2	94	>49:1	−95
13[g]	$Gd(OTf)_3$	**L3**	CH_2Cl_2	92	>49:1	−93
14[g]	$Dy(OTf)_3$	**L3**	CH_2Cl_2	94	>49:1	−93
15[g]	$Er(OTf)_3$	**L3**	CH_2Cl_2	86	>49:1	−94
16[g]	$Yb(OTf)_3$	**L3**	CH_2Cl_2	86	>49:1	−96

[a] Reaction conditions: ligand (5.5 mol%), metal (5 mol%), **1a** (0.12 mmol), **2a** (0.1 mmol), solvent (0.4 mL), 30 °C, 24 h. [b] Yield of the isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] The *ee* value of the opposite configuration is defined as minus. [e] 10 mg of molecular sieves (4 Å) were added. [f] 2 mol% catalyst loading was used. [g] The reaction was carried out in 0.3 mL of solvent at 0 °C for 30 h. Bn = benzyl, Tf = trifluoromethanesulfonyl.

reaction rate. Notably, the catalyst loading could be lowered to 2 mol% without an appreciable drop in reactivity and enantioselectivity (Table 1, entry 5). The optimal reaction conditions were 5 mol% of $Sc(OTf)_3$/**L3** and 10 mg of molecular sieves at 30°C in EtOH.

To investigate the scope of orthogonal enantioselectivity in the catalytic asymmetric Michael addition, we next explored the effect of the metal center. Pleasingly, the yttrium(III)/**L3** system gave the opposite configuration of the product **3a** with excellent diastereoselectivity and moderate enantioselectivity (Table 1, entry 6). A screen of solvents (Table 1, entries 7–9) indicated that the same diastereoselectivity and higher enantioselectivity could be obtained in CH_2Cl_2 (Table 1, entry 9). Furthermore, when the catalyst loading was lowered to 2 mol%, good results could still be obtained (Table 1, entry 10). Although similar results were obtained using many other rare-earth-metal salts (Table 1, entries 11–16), the optimal reaction conditions were established using 5 mol% of $Y(OTf)_3$/**L3** at 0°C to obtain the enantiomer.

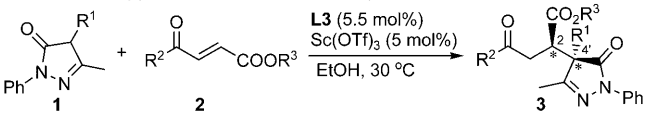
Under the optimized reaction conditions, we examined the scope of the scandium(III)-catalyzed Michael addition of 4-substituted pyrazolones to 4-oxo-4-arylbutenoates (Table 2). The more sterically hindered isopropyl 4-oxo-4-arylbutenoate exhibited better enantioselectivity than ethyl 4-oxo-4-arylbutenoate (compare Table 2, entries 1 and 2), and the reaction proceeded well for many differently substituted alkyl 4-oxo-4-arylbutenoates and 4-substituted pyrazolones, independent of the electron-donating or electron-withdrawing character of the substituents (up to 95% *ee*, 19:1 d.r.). Moreover, heteroaromatic and fused-ring substrates were also applicable, and gave the desired products with good results (Table 2, entries 10, 11, and 15).

We then investigated the Michael addition of 4-substituted pyrazolones and alkyl 4-oxo-4-arylbutenoates in the presence of 5 mol% of $Y(OTf)_3$/**L3** (Table 3) and the corresponding enantiomers were obtained with excellent diastereoselectivity and enantioselectivity (up to 98% *ee*, >49:1 d.r.). The ester groups of the alkyl 4-oxo-4-arylbutenoates exhibited little effect on the enantioselectivity but they did influence the reactivity of the substrates (Table 3, entries 1–4). The enantioselectivity of the reaction was not sensitive to either the steric or the electronic properties of the substituents on the phenyl ring (Table 3, entries 5–12), and the corresponding products were isolated in good yields and excellent enantiomeric excess. In addition, heteroaromatic and fused-ring substrates also reacted well with pyrazolones to deliver the desired products with excellent results (Table 3, entries 13 and 14). Similar to the $Sc(OTf)_3$ system, pyrazolones with different alkyl substituents were also competent substrates, thus providing the Michael addition products with up to 95% yield, greater than 49:1 d.r. and up to 98% *ee* (Table 3, entries 15–21). The absolute configuration of **3k** was determined to be 2*S*,4′*S* by single-crystal X-ray analysis (see Figure 1a).[8]

To test the synthetic potential of the present approach, a gram-scale synthesis of the chiral pyrazolones was performed (Scheme 1). The reaction of 4 mmol of starting materials, under the optimized reaction conditions, produced the desired product without loss of reactivity and enantioselectivity.

To gain insight into the reaction mechanism, we investigated the relationship between the *ee* value of ligand **L3** and the product **3a**. Poor nonlinear effects were observed for both catalytic systems,[9] thus suggesting that minor oligomeric aggregates of $Sc(OTf)_3$/**L3** and $Y(OTf)_3$/**L3** might exist in the reaction system (see the Supporting Information). The effects of the solvent showed that using ethanol lowered the enantioselectivity in the yttrium(III)-catalyzed reaction, however, in the scandium(III)-catalyzed reaction it not only

Table 2: $Sc(OTf)_3$-catalyzed enantioselective Michael addition of 4-substituted pyrazolones **1** to 4-oxo-4-arylbutenoates **2**.[a]



1

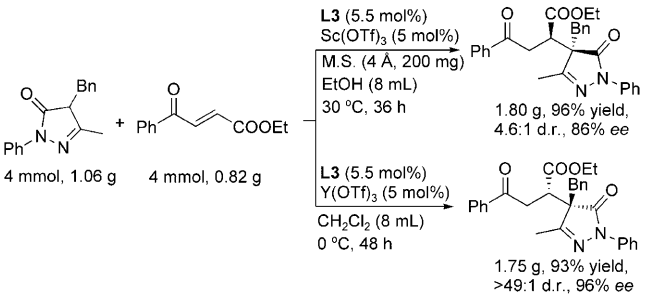
2

3

1a: R^1 = Bn
1b: R^1 = 4-$MeC_6H_4CH_2$
1c: R^1 = 3-$MeC_6H_4CH_2$
1d: R^1 = 4-$MeOC_6H_4CH_2$
1e: R^1 = 3-$MeOC_6H_4CH_2$
1f: R^1 = 2-furanylmethyl
1g: R^1 = allyl
1h: R^1 = Et
1i: R^1 = Me

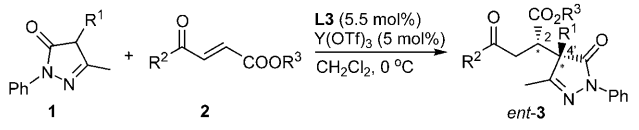
Entry	R^1	R^2	R^3	Yield [%][b]	d.r.[c]	*ee* [%][c]
1	**1a**	Ph	Et	95 (**3a**)	4.6:1	86
2	**1a**	Ph	*i*Pr	83 (**3c**)	9:1	90
3	**1a**	4-MeC_6H_4	*i*Pr	91 (**3e**)	6.7:1	92
4	**1a**	4-FC_6H_4	*i*Pr	85 (**3f**)	6.1:1	94
5	**1a**	4-ClC_6H_4	*i*Pr	95 (**3g**)	7.3:1	93
6	**1a**	4-BrC_6H_4	*i*Pr	96 (**3h**)	4.5:1	93
7	**1a**	4-$MeOC_6H_4$	*i*Pr	85 (**3i**)	5.7:1	92
8	**1a**	3-ClC_6H_4	*i*Pr	83 (**3j**)	13.3:1	92
9	**1a**	3,4-$Cl_2C_6H_3$	*i*Pr	89 (**3k**)	10.1:1	90[d]
10	**1a**	2-thienyl	*i*Pr	95 (**3m**)	3:1	90
11	**1a**	2-naphthyl	*i*Pr	97 (**3n**)	8.1:1	91
12	**1b**	Ph	*i*Pr	91 (**3o**)	9:1	95
13	**1c**	Ph	*i*Pr	97 (**3p**)	4.9:1	90
14	**1e**	Ph	*i*Pr	95 (**3r**)	6.1:1	95
15	**1f**	Ph	*i*Pr	95 (**3s**)	19:1	95
16	**1h**	Ph	*i*Pr	97 (**3v**)	19:1	93
17	**1i**	Ph	*i*Pr	92 (**3w**)	13.3:1	86

[a] Reaction conditions: **L3** (5.5 mol%), $Sc(OTf)_3$ (5 mol%), molecular sieves (4 Å, 10 mg), **1** (0.12 mmol), **2** (0.1 mmol), EtOH (0.4 mL), 30°C, 24 h. [b] Yield of the isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] The absolute configuration was determined to be 2*R*,4′*R* by comparison of the HPLC and optical rotation values (Table 3, entry 11).



Scheme 1. The gram-scale synthesis of **3a** that demonstrates the switch in enantioselectivity. M.S. = molecular sieves.

Table 3: $Y(OTf)_3$-catalyzed enantioselective Michael addition of 4-substituted pyrazolones **1** to alkyl 4-oxo-4-arylbutenoates **2**.[a]



Entry	R^1	R^2	R^3	Yield [%][b]	*ee* [%][c]
1[d]	**1a**	Ph	Et	95 (**3a**)	96
2[d]	**1a**	Ph	Me	93 (**3b**)	90
3	**1a**	Ph	*i*Pr	87 (**3c**)	98
4	**1a**	Ph	Bn	82 (**3d**)	97
5	**1a**	4-MeC_6H_4	*i*Pr	80 (**3e**)	97
6	**1a**	4-FC_6H_4	*i*Pr	84 (**3f**)	98
7	**1a**	4-ClC_6H_4	*i*Pr	91 (**3g**)	97
8	**1a**	4-BrC_6H_4	*i*Pr	95 (**3h**)	98
9[e]	**1a**	4-$MeOC_6H_4$	*i*Pr	75 (**3i**)	91
10	**1a**	3-ClC_6H_4	*i*Pr	91 (**3j**)	97
11	**1a**	3,4-$Cl_2C_6H_3$	*i*Pr	89 (**3k**)	96[f]
12	**1a**	2-ClC_6H_4	*i*Pr	83 (**3l**)	94
13	**1a**	2-thienyl	*i*Pr	82 (**3m**)	95
14	**1a**	2-naphthyl	*i*Pr	91 (**3n**)	97
15	**1b**	Ph	*i*Pr	90 (**3o**)	98
16	**1c**	Ph	*i*Pr	84 (**3p**)	97
17[d]	**1d**	Ph	Et	94 (**3q**)	90
18	**1e**	Ph	*i*Pr	82 (**3r**)	95
19	**1f**	Ph	*i*Pr	87 (**3s**)	96
20	**1g**	Ph	*i*Pr	89 (**3t**)	92
21[d]	**1h**	Ph	Et	93 (**3u**)	83

[a] Reactions conditions: **L3** (5.5 mol%), $Y(OTf)_3$ (5 mol%), **1** (0.12 mmol), **2** (0.1 mmol), CH_2Cl_2 (0.3 mL), 0°C, 48 h. [b] Yield of the isolated product. Generally, >49:1 d.r. was observed. [c] Determined by HPLC on a chiral stationary phase. [d] Reaction time was 30 h. [e] 10 mg of molecular sieves (4 Å) were added and the reaction time was 72 h. [f] The absolute configuration was determined to be 2*S*,4′*S* by single-crystal X-ray analysis.

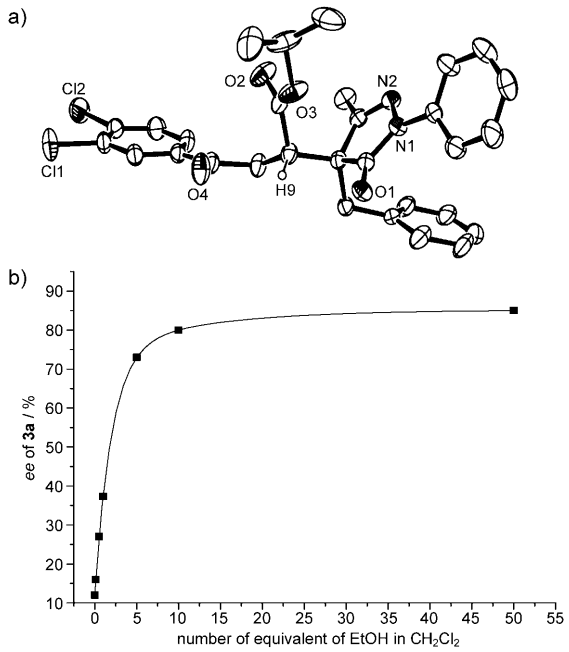


Figure 1. a) X-ray structure of **3k**. Thermal ellipsoids shown at 30% probability (H atoms omitted for clarity). b) Survey of the effect of ethanol as an additive in the $Sc(OTf)_3$/**L3** system.

accelerated the reaction dramatically but also improved the enantioselectivity (Table 1, entries 4–6). Other alcohols also promoted the scandium(III)-catalyzed reaction in satisfactory rates with improved enantioselectivity.[10] Notably, the steric hindrance of the alcohol affected the outcome greatly and bulkier alcohols exhibited lowered enhancement in both the yield (MeOH > EtOH > *i*PrOH > *t*BuOH) and the enantioselectivity (MeOH > EtOH < *i*PrOH > *t*BuOH). Investigations into the use of EtOH as an additive in CH_2Cl_2 showed that the enantioselectivity increased with the addition of EtOH. When 5 equivalents of EtOH were added, the reaction was accelerated and the enantioselectivity improved from 12% *ee* to 73% *ee* (Figure 1b); thus suggesting that the alcohol would plausibly coordinate to the scandium center to participate in the activation of the nucleophile.

Although a detailed mechanistic explanation requires further studies, one interpretation is that the pronounced difference in the ionic radii between scandium(III) and yttrium(III) leads to solvent effects which could be responsible for the switch in enantioselectivity. Scandium(III) has a smaller ionic radius than yttrium(III) (0.754 Å versus 0.93 Å),[11] therefore the alcohol, rather than the sterically hindered pyrazolones, would be expected to coordinate to scandium(III) and the nitrogen atom of the enolized pyrazolone could hydrogen bond to the coordinated alcohol (see the Supporting Information). In contrast, the larger ionic radius of yttrium(III) could allow the coordination of the two reactants to the metal center.[12,13] The unique characteristics of the metal ion, such as the radius and electronic properties, altered the activation pattern and this change created the enantioswitch to give both enantiomers, even in the presence of the same ligand.

In summary, we have successfully developed a highly enantioselective Michael addition of 4-substituted pyrazolones and 4-oxo-4-arylbutenoates, to give a range of 4-substitituted-5-pyrazolone derivatives. By using the ligand **L3**, both enantiomers of the product were obtained in good to excellent enantioselectivities and diastereoselectivities; the respective enantiomers were obtained by changing the metal center. Furthermore, excellent *ee* values and yields can also be obtained in gram-scale reactions, thus showing the potential value of the catalyst system. This method constitutes the first report of a $Sc(OTf)_3$/$Y(OTf)_3$-promoted switch in enantioselectivity in the asymmetric Michael addition of 4-substitituted-5-pyrazolones to 1,4-dicarbonyl but-2-enes and thereby expands the class of reactions amenable to asymmetric catalysis by rare-earth metals. Further investigations into the full reaction scope and mechanism of this catalytic system are still in progress.

Experimental Section

Typical experimental procedure for the Michael addition of 4-substitituted-5-pyrazolones to 1,4-dicarbonyl but-2-enes: **L3** (3.1 mg, 0.0055 mmol), scandium triflate (2.5 mg, 0.005 mmol), **1a** (31.7 mg, 0.12 mmol), and molecular sieves (4 Å, 10 mg) were stirred in EtOH (0.3 mL) under nitrogen at 30°C for 30 min and then **2a** (20.4 mg,

0.10 mmol in 0.1 mL EtOH) was added. The reaction mixture was stirred at 30 °C for 24 h. Then the reaction mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 9:1→5:1) to afford the desired product **3a** in 95 % yield with 86 % *ee* and 4.6:1 d.r.

Received: December 30, 2010
Revised: February 24, 2011
Published online: April 14, 2011

Keywords: asymmetric synthesis · homogeneous catalysis · Michael addition · nitrogen heterocycles · rare-earth metals

[1] For reviews, see: a) M. P. Sibi, M. Liu, *Curr. Org. Chem.* **2001**, *5*, 719; b) G. Zanoni, F. Castronovo, M. Franzini, G. Vidari, E. Giannini, *Chem. Soc. Rev.* **2003**, *32*, 115; c) T. Tanaka, M. Hayashi, *Synthesis* **2008**, 3361; d) M. Bartók, *Chem. Rev.* **2010**, *110*, 1663.

[2] For selected examples, see: a) W.-Q. Wu, Q. Peng, D.-X. Dong, X.-L. Hou, Y.-D. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 9717; b) W. Zeng, G.-Y. Chen, Y.-G. Zhou, Y.-X. Li, *J. Am. Chem. Soc.* **2007**, *129*, 750, and references therein.

[3] For selected recent examples, see: a) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron Lett.* **1996**, *37*, 3815; b) M. P. Sibi, J. J. Shay, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc.* **1998**, *120*, 6615; c) M. P. Sibi, J. Chen, *J. Am. Chem. Soc.* **2001**, *123*, 9472; d) K. Yabu, S. Masumoto, S. Yamasaki, Y. Hamashima, M. Kanai, W. Du, D. P. Curran, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 9908; e) N. Shibata, T. Ishimaru, T. Nagai, J. Kohno, T. Toru, *Synlett* **2004**, 1703; f) J. C. Mao, B. S. Wan, Z. J. Zhang, R. L. Wang, F. Wu, S. W. Lu, *J. Mol. Catal. A: Chem.* **2005**, *225*, 33; g) G. Desimoni, G. Faita, M. Guala, A. Laurenti, M. Mella, *Chem. Eur. J.* **2005**, *11*, 3816; h) D. M. Du, S. F. Lu, T. Fang, J. Xu, *J. Org. Chem.* **2005**, *70*, 3712; i) A. Frölander, C. Moberg, *Org. Lett.* **2007**, *9*, 1371; j) H. Y. Kim, H.-J. Shih, W. E. Knabe, K. Oh, *Angew. Chem.* **2009**, *121*, 7556; *Angew. Chem. Int. Ed.* **2009**, *48*, 7420; k) H. Y. Kim, K. Oh, *Org. Lett.* **2009**, *11*, 5682; l) K. Y. Spangler, C. Wolf, *Org. Lett.* **2009**, *11*, 4724; m) N. Shibata, M. Okamoto, Y. Yamamoto, S. Sakaguchi, *J. Org. Chem.* **2010**, *75*, 5707.

[4] For selected examples of the construction of the skeleton of 4-substituted-pyrazolin-5-ones, see: a) J. B. Field, E. C. Dolendo, A. Mireles, B. H. Ershoff, *Cancer Res.* **1966**, *26*, 1371; b) B. Foth, *Cancer Res.* **1972**, *32*, 804; c) C. K. Ghosh, K. K. Mukhopadhyay, *Synthesis* **1978**, 779; d) B. Chantegrel, S. Gelin, *Synthesis* **1985**, 548; e) V. Colotta, L. Cecchi, F. MeLani, G. Palazzino, G. Filacchioni, *Tetrahedron Lett.* **1987**, *28*, 5165; f) V. Colotta, L. Cecchi, F. Melani, G. Palazzino, G. Filacchioni, C. Martini, G. Giannaccini, A. Lucacchini, *J. Pharm. Sci.* **1989**, *78*, 239; g) R. K. Boeckman, Jr., J. E. Reed, P. Ge, *Org. Lett.* **2001**, *3*, 3651; h) M. Abass, B. B. Mostafa, *Bioorg. Med. Chem.* **2005**, *13*, 6133; i) M. S. Chande, P. A. Barve, V. Suryanarayan, *J. Heterocycl. Chem.* **2007**, *44*, 49; j) G. Mariappan, B. P. Saha, N. R. Bhuyan, P. R. Bharti, D. Kumar, *J. Adv. Pharm. Technol. Res.* **2010**, *1*, 260; k) R. Ma, J. Zhu, J. Liu, L. Chen, X. Shen, H. Jiang, J. Li, *Molecules* **2010**, *15*, 3593; for asymmetric examples with pyrazolinone derivatives, see: l) Y.-H. Liao, W.-B. Chen, Z.-J. Wu, X.-L. Du, L.-F. Cun, X.-M. Zhang, W.-C. Yuan, *Adv. Synth. Catal.* **2010**, *352*, 827; m) S. Gogoi, C.-G. Zhao, *Tetrahedron Lett.* **2009**, *50*, 2252; n) S. Gogoi, C.-G. Zhao, D. Ding, *Org. Lett.* **2009**, *11*, 2249; o) Z. G. Yang, Z. Wang, S. Bai, X. H. Liu, L. L. Lin, X. M. Feng, *Org. Lett.* **2011**, *13*, 596; p) A. N. Alba, A. Zea, G. Valero, T. Calbet, M. Font-Bardía, A. Mazzanti, A. Moyano, R. Rios, *Eur. J. Org. Chem.* **2011**, 1318.

[5] For reviews of catalytic enantioselective construction of quaternary chiral centers, see: a) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473; b) E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11943; c) D. J. Ramón, M. Yus, *Curr. Org. Chem.* **2004**, *8*, 149; d) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688; for selected examples of the catalytic construction of adjacent quaternary and tertiary chiral centers, see: e) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11204; f) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107; *Angew. Chem. Int. Ed.* **2005**, *44*, 105; g) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 2956; *Angew. Chem. Int. Ed.* **2005**, *44*, 2896; h) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482; i) D. J. V. C. van Steenis, T. Marcelli, M. Lutz, A. L. Spek, J. H. van Maarseveen, H. Hiemstra, *Adv. Synth. Catal.* **2007**, *349*, 281; j) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366.

[6] For selected examples with 1,4-dicarbonyl but-2-enes as Michael acceptors, see: a) R. Shintani, K. Ueyama, I. Yamada, T. Hayashi, *Org. Lett.* **2004**, *6*, 3425; b) J. L. Zigterman, J. C. S. Woo, S. D. Walker, J. S. Tedrow, C. J. Borths, E. E. Bunel, M. M. Faul, *J. Org. Chem.* **2007**, *72*, 8870; c) W. P. Ye, Z. Y. Jiang, Y. J. Zhao, L. M. Serena, Y.-P. Goh, D. S. Leow, Y.-T. Soh, C.-H. Tan, *Adv. Synth. Catal.* **2007**, *349*, 2454; d) Z. Jiang, Y. Yang, Y. Pan, Y. Zhao, H. Liu, C.-H. Tan, *Chem. Eur. J.* **2009**, *15*, 4925; e) G. Blay, I. Fernández, A. Monleón, M. C. Muñoz, J. R. Pedro, C. Vila, *Adv. Synth. Catal.* **2009**, *351*, 2433; f) H. Lu, X. Wang, C. Yao, J. Zhang, H. Wu, W.-J. Xiao, *Chem. Commun.* **2009**, 4251; g) Z. Wang, D. H. Chen, Z. G. Yang, S. Bai, X. H. Liu, L. L. Lin, X. M. Feng, *Chem. Eur. J.* **2010**, *16*, 10130.

[7] For our own work in this field, see: a) M. S. Xie, X. H. Chen, Y. Zhu, B. Gao, L. L. Lin, X. H. Liu, X. M. Feng, *Angew. Chem.* **2010**, *122*, 3887; *Angew. Chem. Int. Ed.* **2010**, *49*, 3799; b) Y. F. Cai, X. H. Liu, Y. H. Hui, J. Jiang, W. T. Wang, W. L. Chen, L. L. Lin, X. M. Feng, *Angew. Chem.* **2010**, *122*, 6296; *Angew. Chem. Int. Ed.* **2010**, *49*, 6160; c) W. T. Wang, X. H. Liu, W. D. Cao, J. Wang, L. L. Lin, X. M. Feng, *Chem. Eur. J.* **2010**, *16*, 1664; d) Y. L. Liu, D. J. Shang, X. Zhou, Y. Zhu, L. L. Lin, X. H. Liu, X. M. Feng, *Org. Lett.* **2010**, *12*, 180; e) Y. L. Liu, D. J. Shang, X. Zhou, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2009**, *15*, 2055; f) D. J. Shang, Y. L. Liu, X. Zhou, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2009**, *15*, 3678; g) F. Wang, X. Liu, Y. Zhang, L. Lin, X. Feng, *Chem. Commun.* **2009**, 7297; h) Z. P. Yu, X. H. Liu, Z. H. Dong, M. S. Xie, X. M. Feng, *Angew. Chem.* **2008**, *120*, 1328; *Angew. Chem. Int. Ed.* **2008**, *47*, 1308; i) X. Li, X. H. Liu, Y. Z. Fu, L. J. Wang, L. Zhou, X. M. Feng, *Chem. Eur. J.* **2008**, *14*, 4796; j) K. Zheng, J. Shi, X. H. Liu, X. M. Feng, *J. Am. Chem. Soc.* **2008**, *130*, 15770.

[8] CCDC 798756 (**3k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] a) D. Guillaneux, S. H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, *116*, 9430; b) C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922; c) T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem.* **2009**, *121*, 464; *Angew. Chem. Int. Ed.* **2009**, *48*, 456.

[10] Solvent screening of scandium(III)-catalyzed reaction: CH_2Cl_2: 25 % yield, 70:30 d.r., 12 and 72 % *ee* for the respective diastereomers; CH_3OH: 99 % yield, 81:19 d.r., 80 and 63 % *ee* for the respective diastereomers; C_2H_5OH: 90 % yield, 82:18 d.r., 86 and 90 % *ee* for the respective diastereomers; *i*PrOH: 80 % yield, 80:20 d.r., 67 and 77 % *ee* for the respective diastereomers; *t*BuOH: 60 % yield, 75:25 d.r., 60 and 73 % *ee* for the respective diastereomers (see the Supporting Information).

[11] a) R. D. Shannon, *Acta Crystallogr. Sect. A* **1976**, *32*, 751; b) K. Mikami, M. Terada, H. Matsuzawa, *Angew. Chem.* **2002**, *114*, 3704; *Angew. Chem. Int. Ed.* **2002**, *41*, 3554.

[12] a) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187; b) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, *Chem. Rev.* **2002**, *102*, 2227; for a related concept in lanthanide metals with oxazoline-type ligands, see reference [3g].

[13] The HRMS analysis on the dynamic intermediates showed that the complex $[Y^{3+} + \mathbf{L3} + OTf^- + (\mathbf{1a})\text{-}H^+]^+$ was the main intermediate in the reaction, thus suggesting the possibility that a 4-substitituted-5-pyrazolone serves as a ligand as well as a substrate (see the Supporting Information).

