聚乙二醇负载的二茂铁噁唑啉配体的合成及其应用

刘洪强 [a,b]   时磊 [a]   陈庆安 [a]   王磊*[b]   周永贵*[a]

([a] 中国科学院大连化学物理研究所 大连 116023)

([b] 淮北师范大学 淮北市 235000)

摘要 报道了聚乙二醇(MeO-PEG)负载的二茂铁噁唑啉衍生的手性 N,P 和 N,S 配体的合成. 所得负载 N,P 配体可以成功应用于银催化的[3+2]环加成反应, 最高取得了 97%的对映选择性. 另外聚乙二醇负载二茂铁 N,S 配体可以成功应用于钯催化的烯丙基取代反应, 取得了 90%的 ee 值. 值得注意是, 聚乙二醇负载形成的催化剂循环使用 4 次后其催化活性和选择性仍可基本保持.

关键词 聚乙二醇; 二茂铁噁唑啉; 不对称催化

Synthesis of MeO-PEG-Supported Ferrocenyloxazoline Ligands and Their Application in Asymmetric Catalysis

Liu, Hongqiang[a,b]   Shi, Lei[a]   Chen, Qingan[a]   Wang, Lei*[b]   Zhou, Yonggui*[a]

([a] Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China)
([b] Huaibei Normal University, Huaibei 235000, China)

Abstract A simple synthesis of ferrocenyloxazoline derived chiral N,P ligands and N,S ligands immobilized on a MeO-PEG-support is described. The metal complexes of chiral ligands have been successfully applied to 1,3-dipolar cycloaddition reaction of azomethine ylides and asymmetric allylic substitution reaction, providing the products with up to 97% ee and 90% ee, respectively. The MeO-PEG-supported metal complex catalysts can be recycled easily and reused.

Keywords PEG; ferrocenyloxazoline ligands; asymmetric catalysis

1 Introduction

Recently, asymmetric catalysis with polymer-supported transition metal has attracted a great of interest.[1] A prominent advantage of immobilized chiral catalysts lied in easy catalyst separation and recycle. However, the immobilized ligands or catalysts which were not dissolved in common solvents often display lower enantioselectivity and less efficiency in their catalysis in comparison with their parent counterparts. So soluble polymer-reagents and catalysts have achieved wide recognition and acclaim because that reactions are carried out homogeneously which can lead to the higher rates and better enantioselectivities than catalysts immobilized on solids, and catalyst could be separated from the reaction mixture by filtration, precipitation or extraction.[2,3]

As soluble polymer modified poly(ethylene glycol)s (PEGs) recently emerged as readily functionalized, commercially available polymers that are soluble in some solvents and insoluble in a few other solvents for example ether and n-hexane.[4-13] Recently, the monomethyl ether of PEG (MeO-PEG) has successfully being used for supporting chiral ligands to be transformed in catalysts for some catalytic asymmetric reactions. MeO-PEG has also been employed by us for the immobilization of MeO-PEG-supported tunable axial chiral bisphosphine ligands which were applied in asymmetric hydrogenation of quinolines with up to 92% ee.[14] The catalyst system is air-stable and recyclable.

Recently, ferrocenyloxazoline-based chiral ligands have attracted considerable attention in the past decade due to their ease of preparation, modularity and favorable coordinating properties towards a large variety of metals.[15-17] Among them, planar chiral ferrocenyloxazoline derived chiral N,P ligands and N,S ligands are versatile, and have a wide range of applications in asymmetric catalysis. Very recently, our group mainly focused on chiral bifunctional AgOAc catalyzed asymmetric reactions under the mild neutral condition,[18-20] for examples, asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides, asymmetric Mannich-type reactions and asymmetric aminations.[21-25] Among these reactions, ferrocene-derived chiral N,P and N,S ligands gave the excellent reactivity and enantioselectivity. Furthermore, to the best of our knowledge, few examples on soluble polymer supported ferrocenyloxazoline derived chiral N,P and N,S ligands is

reported.[26,27] To increase the synthetic utility and practicability of these effective ligands in asymmetric catalysis, herein, we report the facile synthesis of soluble polymer MeO-PEG supported ferrocenyloxazoline-derived chiral *N,P* and *N,S* ligands (Figure 1) and their applications in 1,3-dipolar cycloaddition reaction and asymmetric allylic substitution reaction.[28,29]
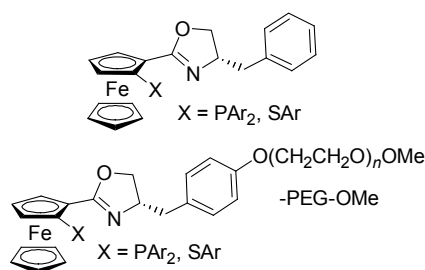

Figure 1 MeO-PEG supported *N,P* and *N,S* ligands

2 Results and discussions

To incorporate the ferrocenyloxazoline ligands into polymer, an additional functional group on the phenyl ring was required, we tried to attach the soluble polymer to 4-position of the phenyl ring. So, the chiral amino alcohol **5** bearing the source of chirality and a function for further linkage to a polymer is the key intermediate. According to a recently published similar procedure,[30,31] (*L*)-Tyrosine is chosen as the starting material, methyl esterification and protection of amino group gave **2**. Then the phenolic hydroxyl group was selectively protected using the TBS, following by reduction by LiAlH$_4$ and removal of the Boc-protecting group to afford the chiral amino alcohol **5** (Figure 2).
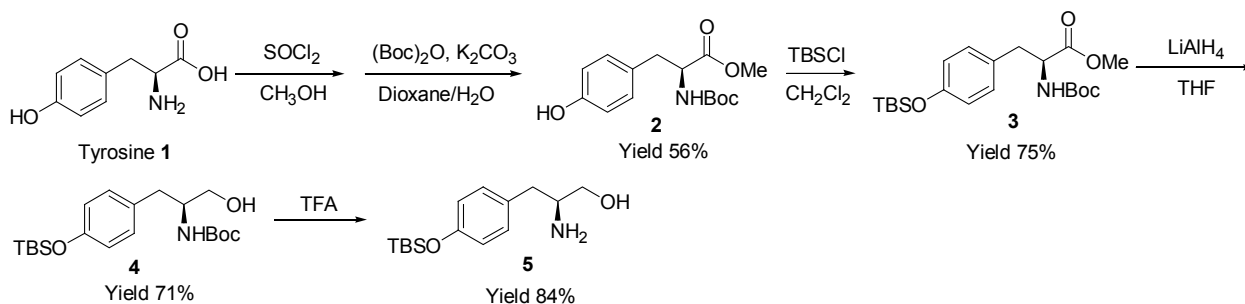
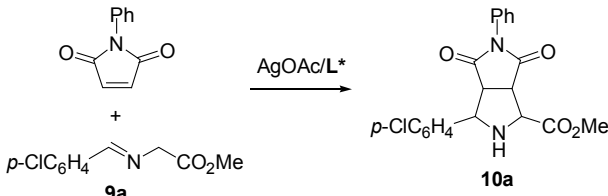According to the known literature procedure,[32] TBS
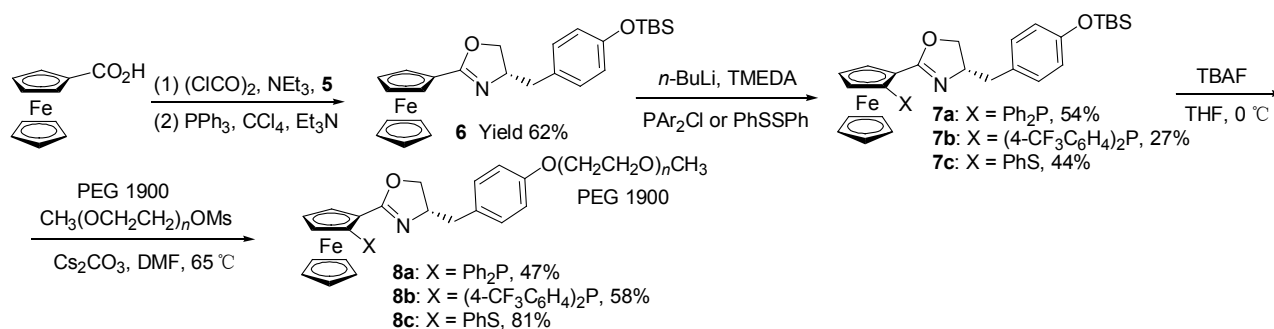
protected oxazoline **6** was conveniently synthesized from ferrocene carboxylic acid and chiral amino alcohol **5**. *ortho*-Lithiation of oxazoline **6** was investigated using *n*-BuLi in Et$_2$O at -78 ℃, followed by addition of Ar$_2$PCl to give the compounds **7** in moderate yields. Then protective group of TBS was removed with TBAF in THF, followed by reaction with poly(ethylene glycol)s 1900 monomethyl ether mesylate in the presence of Cs$_2$CO$_3$ in DMF, giving the PEG supported chiral *N,P* ligands **8a**—**8b** in 47%—81% yields (Figure 3). At the same time, chiral ferrocenyloxazoline derived *N,S* ligand **8c** was also synthesized using the similar literature procedure.[33]

As is known, the pyrrolidine ring is widely present in many biologically active compounds and pharmaceuticals. Furthermore, pyrrolidines are important building blocks in organic synthesis, and have emerged as core structure of privileged organocatalysts in the past years. The [3+2] cycloaddition reaction of azomethine ylide with olefinic dipolarophiles constitutes a straightforward approach to the synthesis of highly substituted chiral pyrrolidine derivatives.[34-50] So far, many laboratories have reported the catalytic asymmetric [3+2] cycloadditions with azomethine ylides by means of a variety of ligand-metal combinations. Our group reported that the ferrocenyloxazoline derived chiral *N,P* ligand showed excellent performance in the Ag(I)-catalyzed enantioselective 1,3-dipolar cycloaddition of azomethine ylides.

To find out whether the MeO-PEG-supported chiral ligands have any influence on the outcome of the reaction, we first tested ligands **8a** in the AgOAc-catalyzed 1,3-dipolar cycloaddition reaction between iminoester **9a** and *N*-phenylmaleimide in toluene. To our delight, we found the cycloaddition reaction finished in 3 h with high activity and excellent enantioselectivity (Entry 1, Table 1). Subsequently, the effect of solvents was examined, and

Figure 2 Synthesis of chiral amino alcohol **5**

Figure 3 Synthesis of MeO-PEG-supported ligands **8**

found THF was the best solvent in view of reactivity and enantioselectivity (Entry 2). So, we selected THF as solvent and examined effect of ligands and temperature. Gratifyingly, an improvement in enantioselectivity (97% *ee*, Entry 5) was observed with ligand **8b** bearing a strong electron-withdrawing trifluoromethyl at the *para* position of the phenyl ring, which is in agreement with our previous result. The slightly lower *ee*s were obtained at 0 ℃ (Entries 6—7). Thus, the optimal conditions for asymmetric cycloaddition of azomethine ylides were AgOAc, **8b**, THF and 25 ℃.

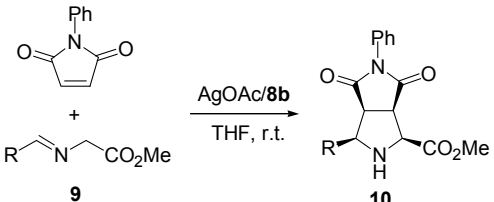**Table 1** Enantioselective 1,3-dipolar cycloaddition of azomethine ylides

Entry[a]	Ligand	Solvent	Temp./℃	Time/h	Yield[b]/%	ee[c]/%
1	**8a**	Toluene	25	3	83	92
2	**8a**	THF	25	4	76	93
3	**8a**	CH$_2$Cl$_2$	25	4	70	89
4	**8a**	Et$_2$O	25	20	64	94
5	**8b**	THF	25	4	95	97
6	**8a**	THF	0	8	89	91
7	**8b**	THF	0	8	92	97

[a] Conditions: iminoester (1.0 equiv.), *N*-phenylmaleimide (1.5 equiv.), AgOAc (3 mol%), ligand (3.3 mol%), concentration (0.12 mol/L). [b] Isolated yields. [c] Determined by HPLC.

On the basis of the optimized reaction conditions, we investigated a variety of iminoester substrates derived from aldehydes with a variety of steric and electronic properties (Table 2). High yields and excellent enantioselectivities were achieved in all of the reactions. The cycloaddition of **9a** gave the best 97% enantioselectivity and 95% isolated yield (Entry 1). For iminoester bearing no substituent, electron-withdrawing substituent, or electron-donating substituent on the benzene ring, the reaction proceeded smoothly in excellent yields and enantioselectivities (Entries 2—4). As for imines bearing an *ortho* group on the benzene ring, the corresponding 1,3-dipolar cycloaddition adducts were obtained in 94% *ee* and 90% *ee*, respectively (Entries 5—6). It is noteworthy that the almost identical enantioselectivity was obtained for the reaction of **9b** with the ligand **8b** and its non-supported mother ligand (Entry 2, 92% vs. 93%).

Then, the recovery and reuse of the MeO-PEG-supported chiral ligand **8b** was studied. We chose the 1,3-dipolar cycloaddition of iminoester **9a** with *N*-phenylmaleimide in THF at room temperature (Table 3). Because MeO-PEG supported ligands **8b** could not dissolve in Et$_2$O and the desired product could dissolve in Et$_2$O, we removed the solvent by oil pump when reaction was completed. Then the system was washed by Et$_2$O until no product was tested under an inert atmosphere. The recovered catalyst could be recycled for four times nearly without a loss in enantioselectivity. It is noteworthy that the
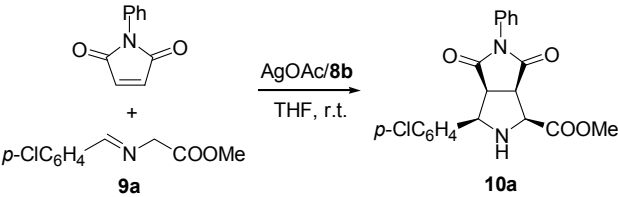
Table 2 Enantioselective 1,3-dipolar cycloaddition of azomethine ylides

Entry[a]	R	Time/h	Yield[b]/%	ee[c]/%
1	4-ClC$_6$H$_4$	2	95 (**10a**)	97
2	Ph	2	90 (**10b**)	92 (93)[d]
3	4-MeC$_6$H$_4$	4	84 (**10c**)	95
4	4-FC$_6$H$_4$	2	93 (**10d**)	92
5	2-MeC$_6$H$_4$	4	86 (**10e**)	94
6	2-ClC$_6$H$_4$	4	92 (**10f**)	90

[a] Conditions: iminoester (1.0 equiv.), *N*-phenylmaleimide (1.5 equiv.), AgOAc (3 mol%), **8b** (3.3 mol%), concentration (0.12 mol/L). [b] Isolated yields. [c] Determined by HPLC. [d] The number in parenthesis was obtained with the non-supported *N,P* ligand. For the detailed information, please see reference [21].

Table 3 Recycling experiments

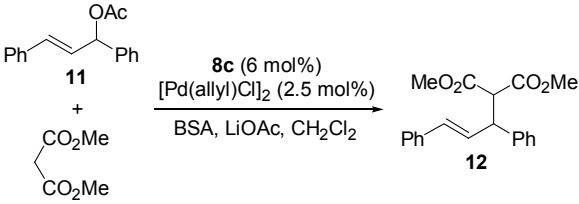| Cycle[a]	Time/h	Yield[b]/%	ee[c]/%
1	4	92	97
2	4	88	95
3	6	92	95
4	6	86	96
5	8	85	95
6	12	74	81

[a] Conditions: iminoester (1.0 equiv.), *N*-phenylmaleimide (1.5 equiv.), AgOAc (3 mol%), **8b** (3.3 mol%), concentration (0.12 mol/L). [b] Isolated yields. [c] Determined by HPLC.

activity slightly decreased, the reaction times were properly prolonged for the satisfied yields (Entries 1—5). But when the catalyst was run in the sixth time, the activities and enantioselectivities decreased remarkably (Entry 6).

The Pd-catalyzed asymmetric allylic substitution is one of the most versatile routes for preparing optically active compounds through carbon-carbon or carbon-heteroatom bond formation.[28,29] Sulfur-nitrogen ligands have recently been proved to be successful in asymmetric allylic substitution.[51] Encouraged by the excellent results obtained in the 1,3-dipolar cycloadditions, we decided to test the catalytic performance of the polymer-supported ferrocenyloxazoline derived *N,S* ligand **8c** in this reaction. The reaction of (*E*)-1,3-diphenylallyl acetate with dimethyl malonate was proceeded in CH$_2$Cl$_2$ using [Pd(allyl)Cl]$_2$ (2.5 mol%)/**8c** (6 mol%) as catalyst and *N,O*-bis(trimethylsilyl)acetamide (BSA) and lithium acetate as base, respectively (Table 4). To our delight, the catalyst still kept its

good enantioselectivity even after being recovered and reused five times. The activity only decreased remarkably in the sixth time.

Table 4 Pd-catalyzed asymmetric allylic alkylation

Cycle[a]	Time/h	Yield[b]/%	ee[c]/%
1	2	95	90
2	2	94	90
3	4	96	88
4	4	94	88
5	4	85	86
6	12	78	85

[a] Conditions: 1 mmol of **11**, dimethylmalonate (3 equiv.), [Pd(allyl)Cl]$_2$ (2.5 mol%), **8c** (6 mol%), LiOAc (5 mol%), BSA (3 equiv.), r.t. [b] Isolated yields. [c] Determined by HPLC.

3 Conclusions

In summary, we have developed an efficient method for the facile synthesis of MeO-PEG-supported ferrocenyl-oxazoline derived chiral *N,P* and *N,S* ligands. These ligands have been successfully applied in asymmetric Ag-catalyzed 1,3-dipolar cycloadditions of azomethine ylides and the Pd-catalyzed asymmetric allylic alkylation with up to 97% *ee* and 90% *ee*, respectively. Furthermore, the MeO-PEG-supported ferrocenyloxazoline ligands can be recovered and reused.

References

[1] Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217.
[2] Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325.
[3] Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345.
[4] Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489.
[5] Han, H. S.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632.
[6] Reger, T. S.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 6929.
[7] Fan, Q. H.; Deng, G. J.; Lin, C. C.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1241.
[8] Li, X. G.; Chen, W. P.; Hems, W.; King, F.; Xiao, J. L. *Org. Lett.* **2003**, *5*, 4559.
[9] Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005**, *7*, 2325.
[10] Xu, L.; Lam, K. H.; Ji, J.; Wu, J.; Fan, Q.-H.; Lo, W.-H.; Chan, A. S. C. *Chem. Commun.* **2005**, 1390.
[11] Yang, X. W.; Liu, H. Q.; Xu, M. H.; Lin, G. Q. *Chin. J. Chem.* **2005**, *23*, 68.
[12] Hu, X. P.; Huang, J. D.; Zeng, Q. H.; Zheng, Z. *Chem. Commun.* **2006**, 293.
[13] Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org. Lett.* **2007**, *9*, 2151.
[14] Wang, X. B.; Zhou, Y. G. *J. Org. Chem.* **2008**, *73*, 5640.
[15] Dai, L. X.; Tu, T.; You, S. L.; Deng, W. P.; Hou, X. L. *Acc. Chem. Res.* **2003**, *36*, 659.
[16] Arrayas, R. G.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7674.
[17] Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505.
[18] Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132.
[19] Yanagisawa, A.; Arai, T. *Chem. Commun.* **2008**, 1165.
[20] Chen, Q. A.; Wang, D. S.; Zhou, Y. G. *Chem. Commun.* **2010**, *46*, 4043.
[21] Zeng, W.; Zhou, Y. G. *Org. Lett.* **2005**, *7*, 5055.
[22] Zeng, W.; Chen, G. Y.; Zhou, Y. G.; Li, Y. X. *J. Am. Chem. Soc.* **2007**, *129*, 750.
[23] Zeng, W.; Zhou, Y. G. *Tetrahedron Lett.* **2007**, *48*, 4619.
[24] Chen, Q. A.; Zeng, W.; Wang, D. W.; Zhou, Y. G. *Synlett* **2009**, 2236.
[25] Chen, Q. A.; Zeng, W.; Zhou, Y. G. *Tetrahedron Lett.* **2009**, *50*, 6866.
[26] Bolm, C.; Hermanns, N.; Classen, A.; Muniz, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1795.
[27] Martin-Matute, B.; Isabel Pereira, S.; Pena-Cabrera, E.; Adrio, J.; Silva, A. M. S.; Carretero, J. C. *Adv. Synth. Catal.* **2007**, *349*, 1714.
[28] Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1.
[29] Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.
[30] Deng, H. B.; Jung, J. K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032.
[31] Liao, L. A.; Zhang, F.; Dmitrenko, O.; Bach, R. D.; Fox, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 4490.
[32] Richards, C. J.; Mulvaney, A. W. *Tetrahedron: Asymmetry* **1996**, *7*, 1419.
[33] You, S. L.; Zhou, Y. G.; Hou, X. L.; Dai, L. X. *Chem. Commun.* **1998**, 2765.
[34] Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
[35] Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484.
[36] Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887.
[37] Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236.
[38] Longmire, J. M.; Wang, B.; Zhang, X. M. *J. Am. Chem. Soc.* **2002**, *124*, 13400.
[39] Chen, C.; Li, X. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174.
[40] Cabrera, S.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394.
[41] Saito, S.; Tsubogo, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 5364.
[42] Chen, X. H.; Zhang, W. Q.; Gong, L. Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652.
[43] Shi, J. W.; Zhao, M. X.; Lei, Z. Y.; Shi, M. *J. Org. Chem.* **2008**, *73*, 305.
[44] Najera, C.; Retamosa, M. D.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6055.
[45] Wang, C. J.; Liang, G.; Xue, Z. Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250.
[46] Wang, C. J.; Xue, Z. Y.; Liang, G.; Lu, Z. *Chem. Commun.* **2009**, 2905.
[47] Xue, Z. Y.; Liu, T. L.; Lu, Z; Huang, H.; Tao, H. Y.; Wang, C. J. *Chem. Commun.* **2010**, 1727.
[48] Kim, H. Y.; Shih, H. J.; Knabe, W. E.; Oh, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7420.
[49] Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338.
[50] Yamashita, Y.; Imaizumi, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 4893.
[51] You, S. L.; Hou, X. L.; Dai, L. X.; Yu, Y. H.; Xia, W. *J. Org. Chem.* **2002**, *67*, 4684.

(Cheng, B.; Lu, Z.)