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A Highly Active Chiral Ruthenium-Based Catalyst for Enantioselective Olefin Metathesis

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Summary: A chiral Ru-based olefin metathesis catalyst bearing a chiral NHC ligand that is both C_1-symmetric and monodentate is described. The catalyst shows increased reactivity in comparison to existing chiral Ru-based catalysts that possess a C_2-symmetric NHC and successfully induces asymmetry in desymmetrization reactions.

Asymmetric ring-closing olefin metathesis (ARCM) has emerged as a powerful method for forming enantiopure carbo- and heterocycles.[1] A variety of different ring-forming processes can be performed using various Mo-based catalysts. However, the development of Ru-based chiral catalysts for ARCM is relatively underdeveloped. In 2001, Grubbs and co-workers reported an elegant strategy in which a chiral relay is used to transfer chirality from the backbone of the monodentate N-heterocyclic carbene (NHC) ligand toward the reactive carbene center.[2] These catalysts have evolved into selective catalysts for the desymmetrization of prochiral trienes.[3] The Hoveyda group has developed a series of catalysts bearing a bidentate NHC ligand which have demonstrated impressive enantioselection in ARCM protocols.[4] These novel NHC ligands bear a phenolate or naphtholate moiety which displaces a Cl ligand in the Ru coordination sphere.[5] Although this lowers the reactivity of the catalyst, it has been demonstrated that through modification of the structure of the precatalyst, sufficient reactivity can be obtained.[5b] Hoveyda and co-workers have attempted to modify the electronics of the naphtholate moiety of the NHC ligand to restore adequate levels of catalyst reactivity.[5b] However, in addition to the aforementioned study, no reports on the structural modification of chiral NHC ligands and their subsequent effect on catalyst reactivity have emerged. Herein we report the preparation of a novel C_1-symmetric, monodentate NHC bearing, Ru-based catalyst with unusual structural characteristics and an increased reactivity profile and its evaluation in the asymmetric desymmetrization of triene reactions.

Our group believed that an increase in enantioinduction in the Grubbs-type catalysts could be obtained if the 1,2-diphenyl backbone of the NHCs was replaced by a 1,2-di-*tert*-butyl unit.[6] This substitution would be made with the hope that the increase in steric bulk would increase the efficiency of the chiral relay

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(1) For recent reviews on asymmetric olefin metathesis, see: (a) Hoveyda, A. H. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, Chapter 2.3. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. (c) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945−950.

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(4) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem*. **2004**, *2*, 8−23.

(5) (a) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2002**, *124*, 4954−4955. (b) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2003**, *125*, 12502−12508. (c) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2005**, *127*, 6877−6882.

(6) For the preparation of **3** see: (a) Alexakis, A.; Mangeney, P.; Roland, S. *Synthesis* **1999**, *2*, 228−230. For a theoretical discussion of the effects of NHC structure on metathesis catalysts see: (b) Occhipinti, G.; Bjorsvik, H.-R.; Jensen, V. R. *J. Am. Chem. Soc*. **2006**, *128*, 6952−6964.

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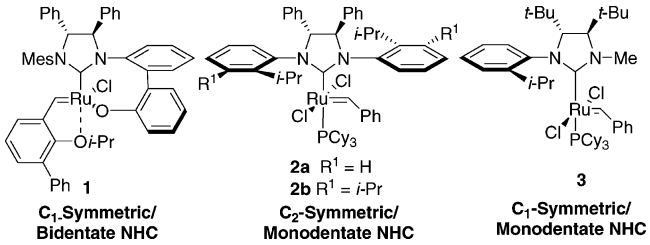
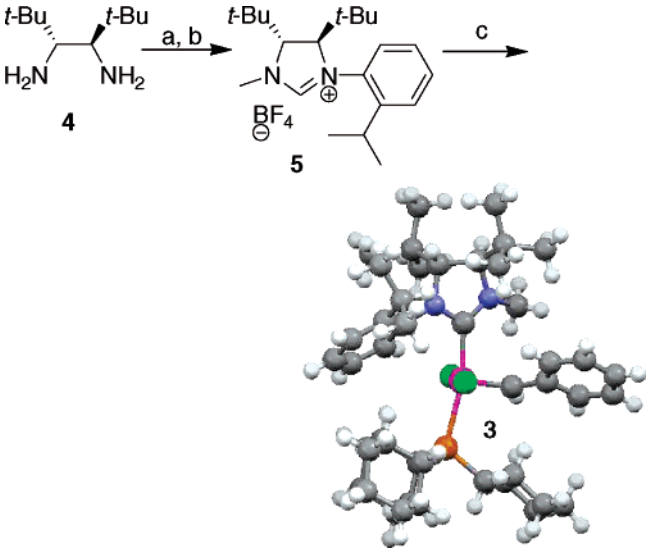


Figure 1. Ru-based asymmetric olefin metathesis catalysts.

Scheme 1. Preparation of Ru-Based Catalyst 3[a]



[a] Reaction conditions: (a) (i) $Pd(OAc)_2$ (5 mol %), (±)-BINAP (10 mol %), NaO-*t*-Bu (3 equiv), 2-isopropylbromobenzene (0.9 equiv), PhMe, Δ, 24−30 h then (ii) Na_2SO_4, CH_2O (37% in H_2O) (4.5 équiv), HCO_2H (cat.), CH_2Cl_2, 15 h, 42% yield over two steps; (b) I_2, $NaHCO_3$, CH_2Cl_2, 20 h then NH_4BF_4, 71% yield; (c) **5** (1.5 equiv), $(CF_3)_2CH_3COK$ (1.5 equiv), PhMe, 60 °C, 6 h, $(PCy_3)_2Cl_2Ru{=}CHPh$ (1.0 equiv), 30% yield.

through an alteration in the degree of rotation of the arene. Coincidentally, the inclusion of *t*-Bu groups along the NHC backbone had been proposed as a strategy to increase the reactivity of Grubbs-type olefin metathesis catalysts.[6b] Fearing that an increasingly bulky NHC ligand could hinder attempts to prepare the catalyst, we considered replacing one arene with a less sterically demanding substituent. Intrigued by the possibility of using a C_1-symmetric NHC, we paid particular attention to the work of Blechert and Ledoux on olefin metathesis catalysts bearing an unsymmetrical NHC ligand.[7] Although the use of C_1-symmetric monodentate NHC ligands could possibly afford a mixture of catalysts with different NHC orientations, reports had demonstrated that similar C_1-symmetric NHC ligands are always oriented so that the N-alkyl group is anti to the Ru carbene. On the basis of the available precedent, we choose to replace an N-aryl group with a Me group.

Consequently, we prepared the chiral monodentate C_1-symmetric NHC ligand **5** (Scheme 1). C_1-symmetric bidentate NHC ligands had already been proven to induce high selectivities in ARCM and in other asymmetric processes,[5c] but the preparation of C_1-symmetric monodentate ligands had not been attempted. When **5** was subjected to established conditions used to prepare Grubbs second-generation-like catalysts,[2,3] catalyst **3** was isolated in 30% yield. During the characterization of the catalyst we observed several unusual spectroscopic features. Following the example of Blechert,[7a] NOE experiments were conducted and demonstrated that the Me group is located directly over the carbene unit, which is in direct contrast to previous reports. This was confirmed via X-ray crystal analysis of **3** (Scheme 1). Although it is difficult to speculate on the interactions that may be responsible for the reversal in NHC geometry, the di-*tert*-butyl backbone of the NHC may cause significant rotation of the N-aryl group to disfavor the association believed to exist between the N-aryl groups of the NHC ligand and the Ph group of the carbene. Interestingly, the carbene moeity of **3** is twisted, placing the carbene proton out of the plane of the chlorine atoms. This slightly tilted and unusual configuration results in an observed coupling to the pendant phosphine in the ^{1}H NMR spectra (doublet, J = 7.5 Hz). Phosphorus decoupling experiments were used to confirm that the coupling of the carbene ^{1}H NMR signal was in fact due to the phosphine.

The fact that the chirality of the NHC ligand was oriented away from the carbene allowed us to test a recent hypothesis regarding the mechanism of enantioinduction of the Grubbs-type asymmetric catalysts. Recent reports from Cavallo et al. have suggested that catalyst **2a** induces enantioselection via the N-aryl group located syn to the carbene unit.[8] Although **3** does not possess a "chiral" group syn to the carbene, Chen and coworkers have shown that dissymmetric Ru catalysts can lead to stereoisomerically distinct carbenes throughout the catalytic cycle in olefin metathesis.[9] Consequently, we decided to evaluate catalyst **5** in a series of desymmetrization of triene reactions (Table 1). We subjected triene **6a** to catalyst **3** under similar reaction conditions optimized for catalysts **2a** and **2b**.[2,3] Indeed, complete conversion of **6a** to **6b** was observed after 2 h at 40 °C in CH_2Cl_2. Surprisingly, catalyst **3** afforded the product **6b** in 81% isolated yield and 82% ee. This level of enantioselectivity is in contrast to that obtained with **2a** or **2b**, which require the addition of NaI as an additive to improve their respective enantioselectivities.

However, when triene **10a** was treated with **3** under identical reaction conditions, the level of conversion was similarly high, but the enantioselectivity in forming **10b** dropped to 33% ee. The formation of six-membered rings proceeded smoothly, albeit in low enantiomeric excess. The heterocycle **7b** was formed in 28% ee using catalyst **3**, while catalyst **2a** in the absence of NaI additive gave **7b** in 76% ee. Catalyst **2a** again proved superior in the formation of the six-membered silicon containing heterocycle **11a** (83% ee vs 5% ee with catalyst **3**). Strangely, catalyst **3** provided much higher ee's for the formation of the seven-membered cycle **8b** (60% ee) compared to the analogous six-membered ring **7b**. Catalyst **3** failed to provide significant yields of the eight-membered ring **9b**; however, even after extended reaction times, **9b** was observed in >95% ee which is greater than the 85% ee observed with **2b** even with NaI as an additive.

Encouraged by the fact that a C_1-symmetric NHC-bearing catalyst could induce asymmetry in desymmetrization reactions, we turned our attention toward catalyst reactivity. Indeed, the effect of a relatively unencumbered N-alkyl unit syn to the

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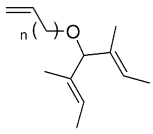
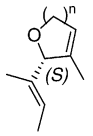
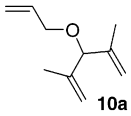
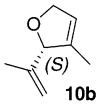
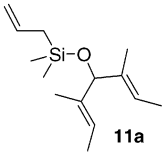
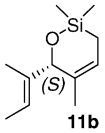
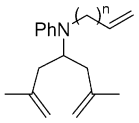
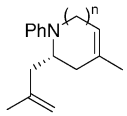
(9) (a) Bornand, M.; Chen, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7909−7911. (b) Christian, A.; Chen, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4484−4487.

Table 1. ARCM Reactions with Chiral Ruthenium Catalysts[a]

triene	product	n	catalyst (mol %)	*ee* (%)[b]	conv (%)[c]	yield (%)[d]
 n= 1, **6a** n= 2, **7a** n= 3, **8a** n= 4, **9a**	 n= 1, **6b** n= 2, **7b** n= 3, **8b** n= 4, **9b**	1	**3** (2.5)	82	>98	81
			2a (2.0)	36	>98	*NR*
			2b (2.0)	46	>98	*NR*
		2	**3** (2.5)	28	>98	81
			2a (2.0)	76	>98	51
		3	**3** (2.5)	60	>98	95
			2b (2.0)	76	93	92
		4	**3** (2.5)	>95[e]	< 5	-
			2b (4.0)[f]	85	< 5	-
 **10a**	 **10b**		**3** (2.5)	33	>98	80
			2a (2.5)	23	96	*NR*
 **11a**	 **11b**		**3** (2.5)	5	>98	82
			2a (2.0)	83	>98	*NR*
			2b (0.8)	92	>98	77
 n= 1, **12a** n= 2, **13a**	 n= 1, **12b** n= 2, **13b**	1	**3** (2.5)	9	*NR*	39
		2	**3** (5.0)[g]	7	*NR*	54

[a] Reactions with **3** were run in CH_2Cl_2, 40 °C, 2 h, [M] = 0.055. *NR* = not reported. *rac* = racemic. [b] Enantiomeric excesses determined by chiral GC: see the Supporting Information for chromatograms. [c] Determined by ^{1}H NMR spectrum of crude reaction mixture. [d] All reactions were run in duplicate, and yields reflect the average isolated yield following chromatography. [e] The reaction mixture was stirred for 24 h. [f] Reaction run in the presence of NaI.[3] [g] **3** added in 2.5 mol % portions/2 h.

reactive benzylidene had yet to be examined in chiral olefin metathesis catalysts.[10] Blechert and Ledoux have observed that catalysts bearing C_1-symmetric NHC ligands in which the N-alkyl group was anti to the carbene afforded reactivities similar to or lower than those of their corresponding parent catalysts.[7a,c] However, it was unknown if a similar affect on the reaction rate would be observed for **3** where the N-alkyl group is syn to the carbene. Consequently, we compared the reactivities of **2a** and **3** in the ring closing of diallyl diethylmalonate (**14**), triene **6a**, and the challenging amine substrate **13a** following guidelines established by Grubbs and co-workers (Figure 2).[11] In the ring closing of **14**, approximately >90% conversion was obtained in just over 5 min with **3**, while approximately 20% conversion had been observed with **2a**. A similar rate increase was observed when comparing the ring closing of **6a**, whereby >90% conversion was obtained in under 10 min with **3** and less than 20% conversion had been obtained with **2a**. In order to further investigate the reactivity of **3**, we performed the desymmetrization of the tertiary amine substrates **12a** and **13a**. To the best of our knowledge, only Mo-based catalysts have been used to effect desymmetrization of these challenging tertiary amine substrates.[12] We were pleased that **3** could afford moderate yields of products **12b** and **13b** using these substrates, although very little enantioselection was observed (Table 1). Gratifyingly, catalyst **3** was once again observed to have greater reactivity toward these amine-bearing substrates. In the ring closing of **13a**, approximately ~40% conversion was obtained in 10 min with **3**, while catalyst **2a** produced approximately <10% conversion. These studies demonstrate that modification of the NHC ligand can lead to an increase in catalyst reactivity and still induce asymmetry. As almost all studies into improving the reactivity of Ru-based metathesis catalysts have centered on varying the structure of the carbene ligand,[13] the NHC modifications concept described

(10) For some recent examples of NHC modification in achiral systems see: (a) Ritter, T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 11768−11769. (b) Berlin, J. M.; Campbell, K.; Ritter, T.; Funk, T. W.; Chlenov, A.; Grubbs, R. H. *Org. Lett.* **2007**, *9*, 1339−1342. (c) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589−1592.

(11) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740−5745.

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(13) (a) Bieniek, M.; Bujok, R.; Cabaj, M.; Lugan, N.; Lavigne, G.; Arlt, D.; Grela, K. *J. Am. Chem. Soc.* **2006**, *128*, 13652−13653. (b) Bujok, R.; Bieniek, M.; Masnyk, M.; Michrowska, A.; Sarosiek, A.; Stepowska, H.; Arlt, D.; Grela, K. *J. Org. Chem.* **2004**, *69*, 6894−6896. (c) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318−9325. (d) Barbasiewicz, M.; Szadkowska, A.; Bujok, R.; Grela, K. *Organometallics* **2006**, *25*, 3599−3604.

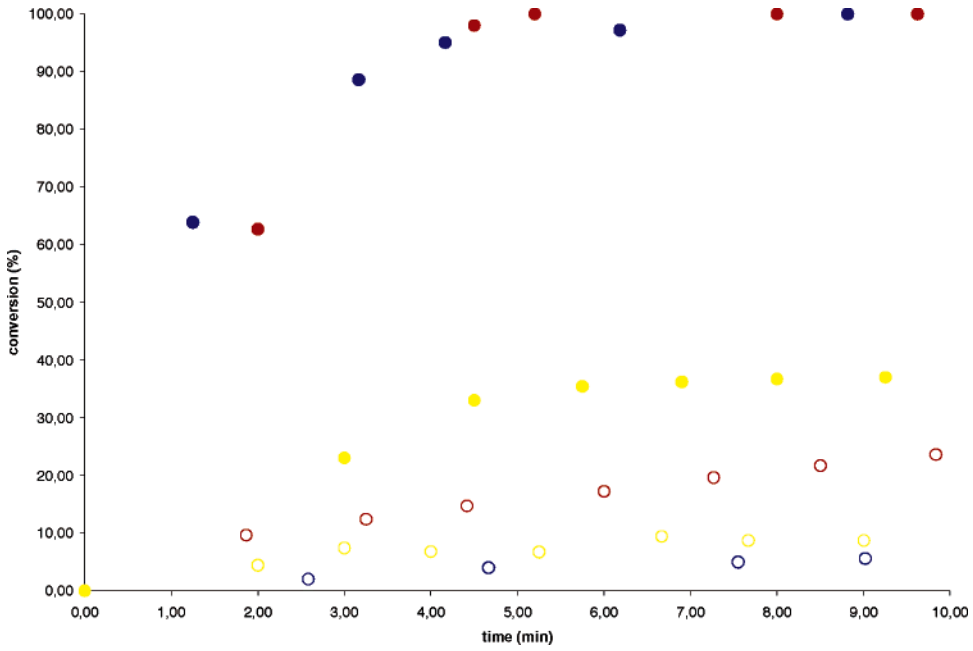

Figure 2. Comparison of the reactivities of **2a** and **3** in three different ring-closing reactions (CD_2Cl_2, 30 °C): ring closing of **6a** (**2a** (blue ○), **3** (blue ●)); ring closing of **14** (**2a** (red ○), **3** (red ●)); ring closing of **13a** (**2a** (yellow ○), **3** (yellow ●)).

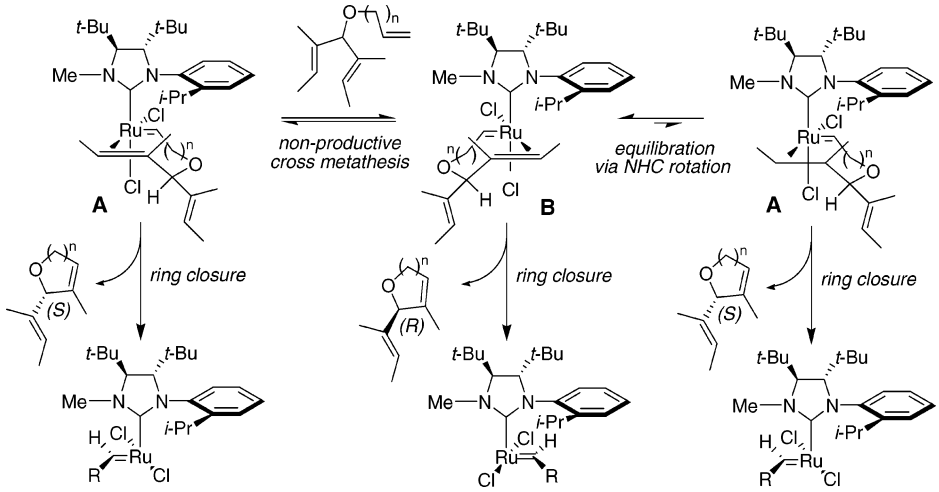

Figure 3. Speculative model for the observed enantioselectivities.

herein should be of interest in the fields of olefin metathesis and catalyst design and in catalysis mediated by NHC ligands.

Recent studies have concluded that it is difficult to generalize whether a side-bound or bottom-bound coordination intermediate is favored, as electronic, steric, and solvent effects each play a significant role.[8b] Presuming that polar solvent effects dominate, we would then propose a model for enantioselection similar to that of Grubbs that includes side binding of the substrate. The intermediate **A** (Figure 3) would undergo metallacyclobutane formation and subsequent ring closure, resulting in the product **6b** having an *S* configuration. However, it is difficult to explain the good ee's obtained for the formation of the five-membered ring **6b** and the seven-membered ring **8b** compared with the poor ee obtained in the corresponding six-membered ring **7b**. If we assume that NHC rotation in the substrate-bound coordination intermediates is slow, then reaction of **3** with **6a** would result in intermediate **A**, where the carbene is now syn to the N-aryl group.[9] If ring closure is fast, the product would be under the influence of the chiral relay in the NHC ligand, thus explaining the good selectivity obtained. In the case of substrate **7a**, ring closure would be slower and might compete with a nonproductive cross-metathesis with another molecule of **7a**. This would now place the alkylidene syn to the *N*-Me group and away from the chiral influence of the NHC ligand, as in intermediate **B**. Subsequent ring closure would result in either poor enantioinduction or a preference for the *R* configuration. In substrate **8a**, the ring closure is expected to be even slower than with **7a**. If this process is slow enough, then NHC rotation may occur to place the N-aryl group in its electronically preferred position syn to the carbene (intermediate **A**). Once again, this conformation would allow for efficient enantioinduction, thus explaining the 60% ee observed for **8b**. It is important to note that this hypothesis is purely speculative and further studies are underway to investigate possible rotation of the NHC ligand during the catalytic cycle.

In summary, the initial investigations of **3** reveal a good selectivity and intriguing reactivity profile. Deciphering the mechanism of enantioinduction for catalyst **3** is likely to produce new insight into the development of more efficient catalysts for ARCM. Optimization of the catalyst structure, application to other ARCM reactions, elucidation of the catalyst's mech-

anism of enantioinduction, and further studies into its reactivity are underway and will be reported in due course.

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Supporting Information Available: Text, figures, and tables giving general procedures and characterization data for the preparation of **3** and data obtained from the kinetic study of **3** and a CIF file giving structural data for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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