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A Chiral Rhodium Carboxamidate Catalyst for Enantioselective C−H Amination

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Catalytic intramolecular C−H amination has advanced as a general technology for chemical synthesis.[1] The utility of the heterocyclic products fashioned from such processes validates efforts to identify chiral transition-metal complexes capable of effecting asymmetric insertion (Figure 1). On a more fundamental level, the challenges associated with the design of a catalytic system able to support a reactive oxidant that can discriminate between two hydrogen atoms on a prochiral methylene center are significant. Nonetheless, success of this type has been realized in enantioselective C−H insertion reactions of diazoalkane derivatives and in select instances involving intra- and intermolecular C−H amination.[2−5] This report describes the development and performance of Rh_2(*S*-nap)$_4$, a valerolactam-derived dirhodium complex that affords some of the highest levels of asymmetric control to date in cyclization reactions of sulfamate esters. The strong preference of this catalyst for promoting allylic C−H bond insertion is also highlighted.

Our earliest efforts to identify chiral catalysts for asymmetric C−H amination focused primarily on dirhodium tetracarboxylate complexes derived from α-amino acids. In all cases examined, cyclized sulfamate products were formed with conspicuously poor enantiomeric induction (0−20% ee). Studies to evaluate % ee as a function of product conversion clearly established that the enantiomeric ratio was decreasing over the reaction time course. Such results are indicative of a change in catalyst structure owing to the lability of the bridging carboxylate groups. Our interest thus turned toward alternative classes of ligands including carboxamide-based designs. In principle, the strongly donating carboxamidate groups increase the capacity of the dirhodium centers for backbonding to the π-acidic nitrene ligand, thus affording a more stable and potentially more discriminating oxidant.[6,7] Unfortunately, simple dirhodium tetracarboxamidate complexes such as Rh_2(cap)$_4$ **1** are ineffective catalysts for C−H amination because of their propensity to undergo facile one-electron oxidation when combined with PhI(OAc)$_2$ or related hypervalent iodine reagents (Figure 2).[8] The resulting mixed-valent Rh^{2+}/Rh^{3+} dimer appears to be catalytically inactive for C−H amination. Accordingly, in order for a dirhodium carboxamide to promote nitrene-mediated insertion, we concluded that its oxidation potential would have to be increased significantly relative to that of Rh_2(cap)$_4$.

The basis for the design of Rh_2(*S*-nap)$_4$ **4** was Rh_2(PTPI)$_4$ **2**, a complex originally developed by Hashimoto for asymmetric alkene cyclopropanation (Figure 2).[9] The measured $Rh^{2+}/Rh^{2+}\rightarrow Rh^{2+}/Rh^{3+}$ redox potential for Rh_2(PTPI)$_4$ is 120 mV vs SCE, marking the rather significant influence of the proximal phthalimide group on the donating strength of the carboxamidate ligand.[10] We reasoned that replacement of the phthalimide moiety with a 2° sulfonamide would allow for intramolecular hydrogen bonding between the N−H and the carbonyl oxygen of the amide, further shifting the rhodium oxidation to higher potential. The recorded CV data for both Rh_2(*S*-nap)$_4$ **4** and its N-methylated analogue **3** confirm this hypothesis (330 and 242 mV, respectively).

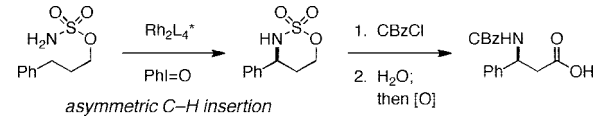
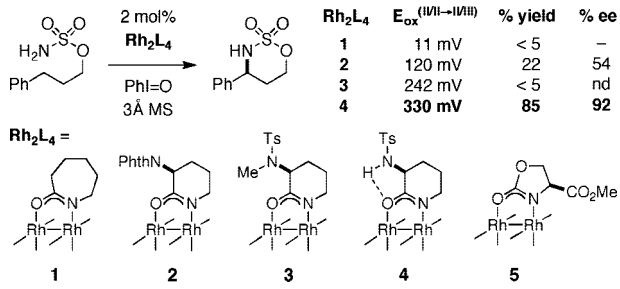


Figure 1. Optically active amine derivatives through C−H amination.



Rh_2L_4	$E_{ox}^{(II/II\rightarrow II/III)}$	% yield	% ee
1	11 mV	< 5	–
2	120 mV	22	54
3	242 mV	< 5	nd
4	**330 mV**	**85**	**92**

Figure 2. Evaluating catalyst performance for C−H amination.

Test reactions with 3-phenylpropylsulfamate, PhI=O, 3 Å molecular sieves, and 2 mol% of the rhodium dimer revealed the importance of the sulfonamide N−H group on catalyst performance (Figure 2). Rh_2(*S*-nap)$_4$ is notably more effective than either Rh_2(PTPI)$_4$ **2** or the N-methylated complex **3**. Although these data appear to show some link between catalyst turnover number and redox potential, other factors are clearly influencing the efficiency of this process. This fact is exemplified with Rh_2(4*S*-MEOX)$_4$ **5**, a complex that has a relatively high oxidation potential of 742 mV but affords <10% of the cyclized product under standard reaction conditions.[7] In comparison to Rh_2(*S*-nap)$_4$, the architecture of the 4*S*-MEOX ligand severely crowds the axial sites on the rhodium centers. It is our feeling that steric effects between the ligands and substrate are exacerbated in the 4*S*-MEOX system, thus adversely affecting the rate of the C−H insertion event and, in turn, the overall performance of the reaction.

Rh_2(*S*-nap)$_4$, is an effective catalyst for oxidation reactions with 3-aryl-substituted propylsulfamate esters (Table 1). Enantiomeric excesses are generally >80%, and the conditions tolerant of most common functional groups. In one case, the isolated heterocycle (entry 1) has been converted to the corresponding (*S*)-*N*-CBz-β-amino acid following a two-step protocol (see Figure 1).[11] This correlation establishes the absolute stereochemistry of the product in entry 1 as *S*.[12,13]

Cognizant of the fact that aziridination of homoallyl sulfamates is highly favored with Rh−tetracarboxylate catalysts, we were surprised to observe the five-membered sulfamidate as the major product in the reaction promoted by Rh_2(*S*-nap)$_4$ (entry 1, Table 2).[1b] This particular result is striking given the strong preference for sulfamate esters to yield six-membered ring heterocycles and the fact that the closely related Rh_2(PTPI)$_4$ catalyst affords primarily the aziridine. The bias for Rh_2(*S*-nap)$_4$ toward allylic insertion

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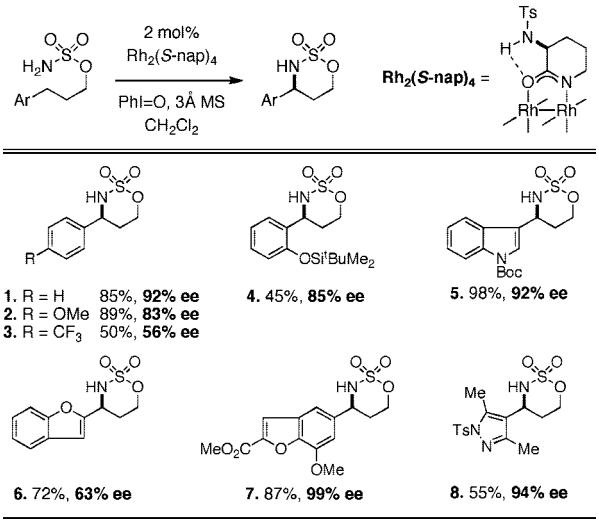
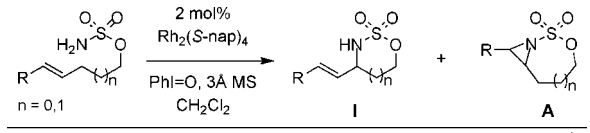
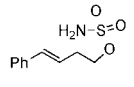
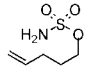
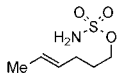
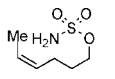
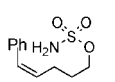
Table 1. Enantioselective Cyclization of Sulfamate Esters[a]



[a] Reactions conducted for 2 h with 2 mol % $Rh_2(S\text{-nap})_4$, 1.2 equiv PhI=O, and 3 Å powdered MS in CH_2Cl_2. Enantiomeric excess (% ee) determined by chiral HPLC analysis. In two cases (entries 4 and 8) 4 mol % catalyst was used.

Table 2. Chemoselective Allylic C−H Bond Insertion



Entry	Substrate	Catalyst	Ratio I/A[a]	Yield I	% ee[b]
1		$Rh_2(OAc)_4$	1:20		
		$Rh_2(PTPI)_4$	1:3		
		$Rh_2(S\text{-nap})_4$	2:1	**48**	12
2		$Rh_2(OAc)_4$	1:1		
		$Rh_2(S\text{-nap})_4$	>20:1	**43**	13
3		$Rh_2(OAc)_4$	2:1		
		$Rh_2(S\text{-nap})_4$	>20:1	**51**	54
4		$Rh_2(OAc)_4$	1:1		
		$Rh_2(S\text{-nap})_4$	>20:1	**48**(70)[c]	82
5		$Rh_2(OAc)_4$	2:1		
		$Rh_2(S\text{-nap})_4$	>20:1	**55**	84

[a] Product ratio determined by ^1H NMR of the unpurified reaction mixture. [b] Enantiomeric excess (% ee) determined by chiral HPLC analysis. [c] Yield in parentheses obtained with 4 mol % catalyst.

appears to be general, occurring with both styrenyl and non-styrenyl olefins. Cis olefins perform optimally in these reactions to give vinyl-substituted oxathiazinanes with enantiomeric excesses >80%. Although levels of asymmetric induction are modest for trans and terminal olefins, allylic C−H insertion is still favored.

The remarkable influence of $Rh_2(S\text{-nap})_4$ on chemoselectivity intimates a possible change in mechanism from the concerted-asynchronous nitrene pathway generally accepted for dirhodium tetracarboxylate-promoted reactions (e.g., $Rh_2(OAc)_4$).[14,15] To test for the possibility that a stepwise, radical C−H abstraction/rebound may be operative, a cyclopropane clock substrate was submitted to the amination protocol (Figure 3). No products of cyclopropane

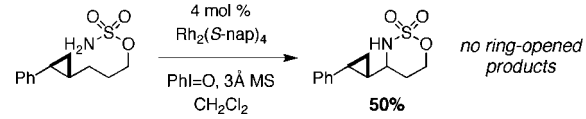


Figure 3. Results suggestive of a concerted insertion mechanism.

ring opening are obtained from this reaction, a result consistent with a concerted, nitrene-type oxidation.[16]

$Rh_2(S\text{-nap})_4$ displays unprecedented performance for the enantioselective intramolecular amination of benzylic and allylic C−H bonds. Despite our still nascent understanding of the factors that influence catalyst turnover numbers and asymmetric control, the design and development of this unique dirhodium complex should further advance methods for C−H functionalization. Continued efforts in this laboratory will attempt to elucidate the nuanced relationship between oxidation potential, ligand structure, and substrate design on catalytic function.

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Supporting Information Available: General experimental protocols and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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