Published in final edited form as:

Chem Commun (Camb). 2009 July 14; (26): 3910–3912. doi:10.1039/b902878a.

Rhodium Catalyzed Enantioselective Cylization of Substituted Imidazoles via C–H Bond Activation†

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Abstract

The enantioselective intramolecular alkylation of substituted imidazoles with enantiomeric excesses up to 98% has been accomplished by rhodium catalyzed C–H bond functionalization with (S,S',R,R')TangPhos as the chiral ligand.

Carbon-hydrogen and carbon-carbon bonds represent the two most common linkages in organic chemistry. Thus, the formation of C–C bonds via catalytic activation of C–H bonds has the potential to be highly general, practical and atom economical. Great progress has been achieved in this area from fundamental study to chemical application.¹ However, only a limited number of catalytic enantioselective transformations have been reported to date. The two most common methods for asymmetric C–H functionalization have been via chelation-assistance² or carbenoid insertion.^{3,4} Our group previously disclosed a unique C-2 functionalization of benzimidazoles that proceeds through a *N*-heterocyclic carbene intermediate obtained via C–H activation.⁵ Herein, we disclose a catalytic asymmetric benzimidazole functionalization that provides remarkably high enantioselectivities (up to 98%) despite the elevated temperatures (135 °C) of the reaction.

Investigation into the catalytic asymmetric alkylation of imidazoles began with *N*-allylic benzimidazole **1** as the model substrate. Reaction parameters were adapted from previously reported conditions for the alkylation of this substrate with achiral catalysts.^{5a} With [RhCl(*coe*)₂]₂ (*coe* = *cis*-cyclooctene) as the rhodium pre-catalyst, a variety of chiral ligands were screened to explore reactivity and enantioselectivity.

Results obtained using a representative subset of screened chiral ligands are summarized in Scheme 1. Monodentate ligands were initially explored (**L1–4**) because only this type of ligand architecture provided successful reactions in past alkylation studies.⁵ Phosphoramidites and phosphites (**L1–2**), which were successful in asymmetric imine directed alkylations, were not active for this system.^{2b,c} Previous work into the alkylations of imidazoles established that

†Electronic Supplementary Information (ESI) available: Experimental details, analytical data, HPLC chromatograms, NMR spectra, and X-ray crystallographic data. See DOI: 10.1039/b000000x/

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electron rich phosphines were required.⁵ Indeed, trialkyl phosphine **L4** provided the desired product in good yield, but in racemic form.

Given the limited number of chiral, monodentate electron rich phosphines that are commercially available, hemi-labile bidentate ligands were explored (**L5-8**). Though from past studies, bidentate ligands consistently inhibited the reaction most likely by blocking a necessary metal coordination site,^{5d} we hoped that the weaker coordination of the nitrogen or oxygen heteroatom on the hemilabile ligands would allow partial dissociation. This hypothesis seemed to be operative as some ligands in this class (**L8**) did generate the cyclized product, albeit in nearly racemic form.⁶

Although we were encouraged by the reactivity of some hemilabile ligands, the chiral induction was still deficient and therefore more rigid chiral bidentate phosphines were explored in hopes of improving ee. Indeed, **L9**, the bidentate analogue of **L4**, did provide the cyclized product with moderate enantioselectivity. However, the bidentate ligand architecture suppressed the reaction, possibly by occupying a metal coordination site necessary for the reaction. Next, the electron rich diphosphine **L12** ((*S,S',R,R'*)-TangPhos) was evaluated.⁷ Not only was high reaction conversion observed, but exceptional enantioselectivity was also achieved, which is notable considering the elevated reaction temperature (135 °C). Interestingly, the close analogue (*S,S',R,R'*)-DuanPhos(**L11**) showed no activity for the alkylation of **1**. Furthermore, a less bulky isopropyl analogue of **L12** resulted in only trace reaction.

Considering the results from the ligand screen, electron rich phosphines seem to be necessary for activity though it is not the only requirement. Partial ligand dissociation to form a monodentate diphosphine may be occurring with **L12** to allow for the formation of an open coordination site necessary to provide catalytic activity.⁸ This process may be slow for **L9** and inaccessible for **L11** or the **L12** analogue. Moreover, the factors that determine the degree of chiral induction are unclear. Of the ligands that were evaluated, only TangPhos incorporated all of the characteristics necessary for a successful and highly enantioselective transformation.

With the identification of TangPhos as an active and selective ligand, reaction optimization was performed to establish THF as the optimal solvent and a slight excess of rhodium to Tangphos as the optimal stoichiometry (Table 1, entry 1). With these optimized conditions identified, substrate scope was next explored. The reaction conditions accommodated the alkylation of isomerizable and aryl substrates (entries 2-3). Electronic effects for aryl substituted alkenes and for the benzimidazole ring were also examined (entries 4-9). Both electron-poor and rich substrates required higher temperatures for satisfactory reaction rates, leading to an erosion of enantioselectivity. Finally, the 4,5-diphenyl substituted imidazole could also be alkylated with high enantioselectivities (entry 10), although alkylation was not observed for the corresponding 4,5-dimethyl imidazole (not shown). Yields were high for most of the substrates. Starting material and products arising from hydrogenation of the starting alkene comprised the remaining mass balance. Alkylation could also be successfully carried out with 2.5% of [RhCl(coe)₂]₂ and 4.9% of TangPhos. Comparable yields (95% by NMR) and only a slight reduction in enantioselectivity (90%) were obtained by performing the cyclization of **1** with this catalyst loading at 175 °C for 36 h.

In summary, a method for the catalytic asymmetric cyclization of substituted imidazoles via C–H bond activation has been achieved. A ligand screen identified TangPhos (**L12**) as a highly active ligand for the asymmetric cyclization of *N*-allylic imidazoles to yield products with moderate to high enantioselectivities even at elevated temperatures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We acknowledge the support by the National Institutes of Health under Grant GM069559 (JAE) and the Office of Basic Energy Sciences, Chemical Sciences Division, U.S. Department of Energy, under Contract DE-AC02-05CH11231(RGB).

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Scheme 1.
Representative chiral ligands screened for enantioselective cyclization of **1**.

Table 1

Substrate scope for the catalytic, asymmetric alkylation of imidazoles.^a

Entry	Product	Temp (°C) Time (h) Yield (%) ^{b,c} ee (%) ^d		
1		135	20	89
				98

Entry	Product	Temp (°C)	Time (h)	Yield (%)	<i>b</i> , <i>c</i>	ee (%)	<i>d</i>

3		135	46	91			97
4		175	24	83			87

<div> </div>		Temp (°C) Time (h) Yield (%) ^{b,c} ee (%) ^d			
Entry	Product				
5		175	24	87	79
6		175	36	89	71
7		175	24	92	81
8		175	24	83	53
9		175	24	81	71

Entry	Product	Temp (°C)	Time (h)	Yield (%)	<i>b,c</i>	ee (%)	<i>d</i>
<p>10% [RhCl(coe)₂]₂ 19% (S,S',R',R')-TangPhos (L12)</p> <p>THF (1M) 135-175°C</p>
10		135	98	90	<i>b,c</i>	95	

^a Absolute configuration of the HCl salt of **2** was determined by X-ray crystallography (see Supporting Information). Remaining products are assigned by analogy.

^b Reactions were carried out on 0.15 mmol scale.

^c Isolated yield after chromatography.

^d Determined by chiral HPLC analysis (see supporting information).