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Rhodium(II)-Catalyzed Enantioselective C−H Functionalization of Indoles

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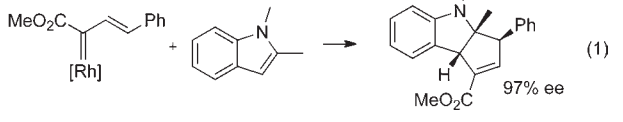
Supporting Information

ABSTRACT: A catalytic, enantioselective method for the C−H functionalization of indoles by diazo compounds has been achieved. With catalytic amounts of Rh_2(*S*-NTTL)$_4$, the putative Rh−carbene intermediates from α-alkyl-α-diazoesters react with indoles at C(3) to provide α-alkyl-α-indolylacetates in high yield and enantioselectivity. From DFT calculations, a mechanism is proposed that involves a Rh−ylide intermediate with oxocarbenium character.

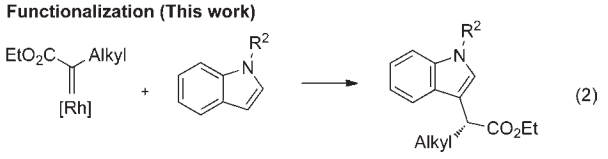
Indoles are important structural motifs in a myriad of biologically interesting natural products and pharmaceutical targets.[1] Accordingly, several methods have been developed for the generation of highly functionalized indoles.[2] Among these strategies is the selective functionalization by metal carbenes derived from α-diazocarbonyl compounds,[3] a reactivity pattern that has been utilized in various total syntheses[4] as well as selective tryptophan modification in peptides and proteins.[5] However, the only catalytic enantioselective reaction of indoles and transient metal carbenes is Davies's [3+2] annulation of indoles with styryldiazoacetates (eq 1).[6] While indol-3-yl acetate derivatives with stereogenic centers positioned α to C-3 have high medicinal value,[1e,1f] only one example of an enantioselective C−H functionalization reaction of an indole has been reported, and the ee was <5%.[6] Described herein is a general Rh-catalyzed method for enantioselective C−H functionalization of indoles by carbenoids derived from α-alkyl-α-diazoesters (eq 2).

[3 + 2] Annulation (Davies)



(1)

C–H Functionalization (This work)



(2)

During the course of our studies on the development of Rh-catalyzed reactions of α-alkyl-α-diazoesters that are selective over β-hydride elimination,[7] we reported a method for enantioselective cyclopropanation of olefins.[7a] The most effective catalyst for enantioselective cyclopropanation was dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] [Rh_2(*S*-PTTL)$_4$], a catalyst first described by Hashimoto.[8] We[7a] and Charette[9] have independently observed that Rh_2(*S*-PTTL)$_4$ and several other phthalimide-derived complexes crystallize in the "chiral crown" conformation. This conformation, in which the four phthalimide groups are projected on one face of the complex, has also been recently observed in crystalline Cu_2(*S*-PTTL)$_4$[10] and dirhodium(II) tetrakis[*N*-(1,8-naphthaloyl)-(*S*)-*tert*-leucinate [Rh_2(*S*-NTTL)$_4$].[10,11] Models for asymmetric induction based on chiral crown conformations have been proposed[7a,9] and debated,[12] and factors that create bias for the chiral crown configuration over competing conformations have been discussed.[7a,9,10] With this foundation, we hypothesized that enantioselective reactions between indoles and α-alkyl-α-diazoesters could be catalyzed by Rh complexes proposed to adopt chiral crown conformations.

We began our investigation with the reaction of 1,2-dimethylindole with a 2-fold excess of ethyl 2-diazohexanoate (Table 1). A variety of Rh complexes derived from *tert*-leucine were screened, as were Rh_2(*S*-DOSP)$_4$ and Rh_2(*R*-PTAD)$_4$. While many of the catalysts screened gave **1** with good enantioselectivity, it was found that Rh_2(*S*-NTTL)$_4$ in toluene at −78 °C was optimal in terms of both yield and enantioselectivity, as **1** was formed in 95% yield and 95% ee. In line with our previous observations,[7] the use of low temperature was critical to the success of the reaction: the analogous reaction at higher temperature (0 °C) gave **1** in only 36% yield and 85% ee (entry 7).

With the optimized reaction conditions in hand, we then explored the scope of this transformation, and the results are summarized in Table 2. High yields (82−96%) and enantioselectivities (79−99% ee) are obtained across a wide array of substrates. Diazoesters bearing a variety of α-alkyl substituents, covering the range of methyl, ethyl, butyl, and isopentyl, led to functionalized indoles with high yield and enantioselectivity. Diazoesters with primary α-alkyl substitutents gave higher enantioselectivity than ethyl α-diazopropionate (compare **9** and **10**). The transformation is successful for reactions of indoles with a range of functionality, including fluoro-, bromo-, methoxy-, siloxy-, Boc-protected aniline and ester functional groups. Methyl (compounds **1**, **2**, **5**, **8**), benzyl (compounds **3**, **4**, **6**, **7**), and aryl (compounds **9**−**15**) groups on nitrogen were well tolerated, while indole itself gave the product of N−H insertion in low enantiomeric excess.[13a] An attempt to react ethyl α-diazo-5-methylhexanoate with 1,3-dimethylindole was also unsuccessful: only intramolecular β-elimination was observed.

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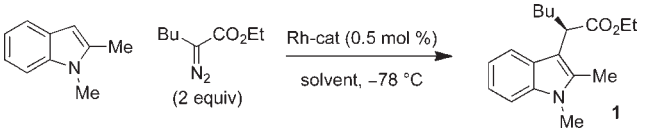
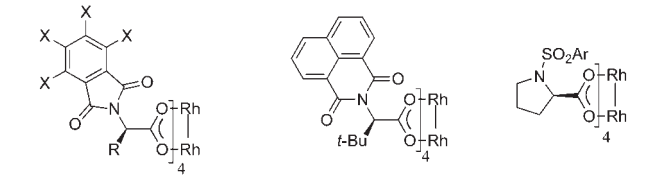
Table 1. Selected Enantioselective Indole Functionalization Optimization Experiments[a]



entry	solvent	catalyst	yield (%)[b]	ee (%)[c]
1	PhMe	Rh_2(*S*-PTTL)$_4$	73	85
2	PhMe	Rh_2(*S*-TCPTTL)$_4$	20	76
3	**PhMe**	**Rh_2(*S*-NTTL)$_4$**	**95**	**95**
4	PhMe	Rh_2(*R*-PTAD)$_4$	54	−91
5	PhMe	Rh_2(*S*-DOSP)$_4$	24	20
6	CH_2Cl_2	Rh_2(*S*-NTTL)$_4$	56	92
7[d]	PhMe	Rh_2(*S*-NTTL)$_4$	36	85

[a] Conditions: indole (0.2 M), Rh-cat (0.5 mol %) at −78 °C, α-diazoester (0.67 M) added via syringe pump. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Reaction run at 0 °C. Optimal conditions in bold.

Catalysts Screened:



Rh_2(*S*-PTTL)$_4$ R = *t*-Bu, X = H
Rh_2(*S*-TCPTTL)$_4$ R = *t*-Bu, X = Cl
Rh_2(*S*-PTAD)$_4$ R = 1-adamantyl, X = H

Rh_2(*S*-NTTL)$_4$

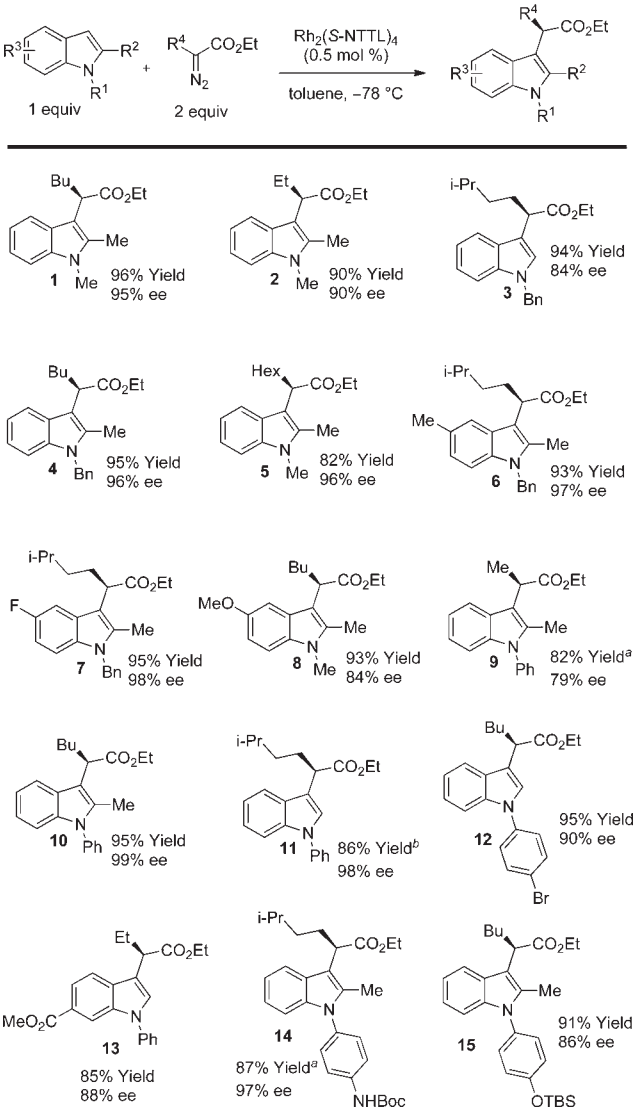
Rh_2(*S*-DOSP)$_4$ Ar = 4-$C_{12}H_{26}$Ph

The nucleophilicity of the nitrogen atom plays a critical role. While the reaction is successful for *N*-aryl or *N*-alkyl indole derivatives, substituting strongly electron-withdrawing groups on nitrogen (e.g., acetyl or Boc) completely shut down the intermolecular reaction, and only the products of β-hydride elimination of the carbenoid were observed. The reaction was also highly sensitive to steric bulk at the indole C(2) position. High yields and enantioselectivities were obtained when R^2 was small (R^2 = H, Me); the highest enantioselectivities were generally observed when R^2 = Me. Experiments with larger R^2 substituents (Et, *n*-Bu, CF_3, Ph, I) were unsuccessful. However, indoles with *N*-to-C(2) ring fusion were excellent substrates, and compounds **16** and **17** were obtained in good yield and high enantioselectivity[13b] (Scheme 1).

Previous mechanistic proposals for the indole C−H functionalization reaction include a cyclopropanation/fragmentation pathway[3b,3c] or an ylide formation/proton-transfer pathway.[3d,3e,6] To rule out the former pathway, we carried out the reaction between indole **18** and ethyl α-diazohexanoate in the presence of racemic **19** and **20**. Compounds **19** and **20** were prepared as an inseparable 1:1 mixture from the Rh_2(Piv)$_4$-catalyzed reaction between 1-phenylindole and ethyl α-diazo-5-methylhexanoate. In the event, Rh_2(*S*-NTTL)$_4$ catalyzed the formation of **8** in 89% yield and 84% ee, and compounds **19** and **20** were isolated in a 1:1 ratio with 97% mass recovery (Scheme 2). That cyclopropane **20** did not rearrange under the reaction conditions provides evidence against the cyclopropanation/fragmentation mechanism.

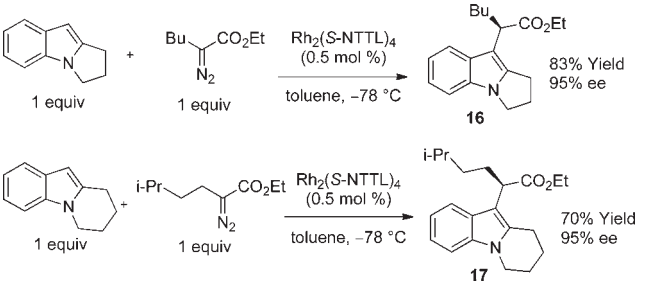
To investigate the plausibility of a mechanism that involves a Rh−ylide, calculations were carried out for the reaction between

Table 2. Scope of the Reaction[c]



[a] 5 equiv of diazoester was used. [b] Contained <5% of the product of alkene cyclopropanation. [c] All yields and ee's refer to the average of two runs.

Scheme 1. Reactions of Fused Indoles



2-methylindole and Et(EtO$_2$C)C=Rh_2(O$_2$CH)$_4$ using the B3LYP method with two basis sets: lanl2dz for Rh and 6-311+G(d,p) for other atoms. A lanl2dz effective core potential was utilized. The calculations support the mechanism shown in

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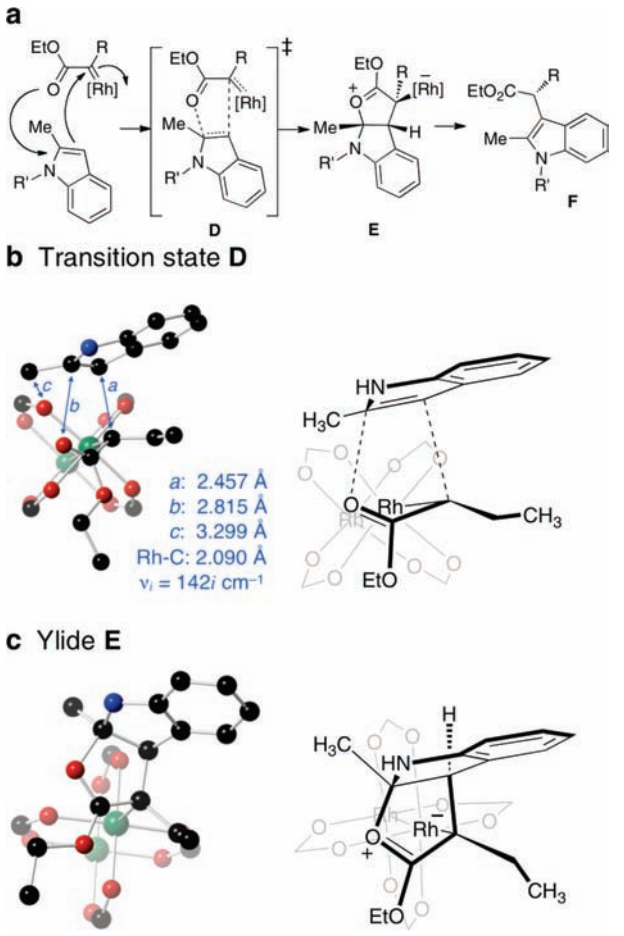

Figure 1. (a) Proposed mechanism. (b) Calculated transition state (**D**) for the reaction between 2-methylindole and Et(EtO$_2$C)C═Rh$_2$(O$_2$CH)$_4$. (c) Calculated structure of ylide **E**.

Scheme 2. Evidence against a Cyclopropanation/Fragmentation Mechanism

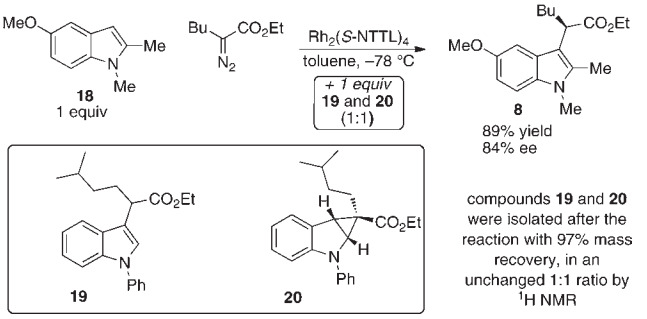

Figure 1a, in which the intermediate ylide **E** is a stabilized oxocarbenium ion formed via transition state **D**. Relative to a pre-reaction complex between the carbene and indole, transition state **D** has a barrier of $\Delta E(\mathrm{ZPE})^{\ddagger}$ = 8.8 kcal/mol (Figure 1b), and the formation of ylide **E** is exothermic by E(ZPE) = 16.0 kcal/mol. Transition state **D** is formed by end-on approach[14] of the indole to the carbene, with only a minor change in the Rh−Rh bond length in **D** (2.498 Å) relative to the carbene (2.490 Å). While both C−C and C−O bonds are formed in this process, the advancement of these bond formations is not

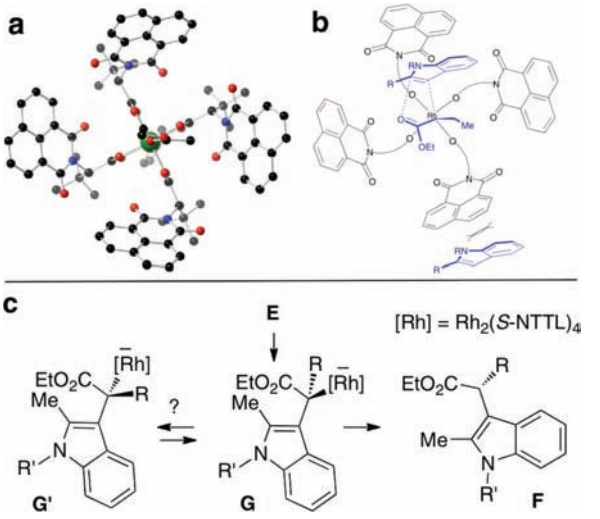

Figure 2. (a) X-ray crystal structure of Rh$_2$(*S*-NTTL)$_4$. (b) Asymmetric induction may be explained by approach of the indole to the *si*-face of the Rh−carbene, with subsequent aromatization and stereoretentive protonation. (c) Alternatively, asymmetric induction may occur via dynamic kinetic resolution, provided that equilibrium between diastereomeric Rh−enolates **G** and **G′** is fast relative to the rate of protonation.

synchronous. Thus, the C−C distance (2.457 Å, labeled *a* in Scheme 2b) in **D** is considerably shorter than the C−O bond distance (2.815 Å, labeled *b* in Figure 1b) in transition state **D**. By contrast, the corresponding distances in ylide **E** (Scheme 2c) are 1.542 and 1.501 Å, respectively.

In transition state **D**, the C-1 methyl group projects toward one of the formate ligands (3.299 Å separation, labeled *c* in Figure 1b), whereas the nitrogen substituent projects away from the Rh−carboxylate core. Thus, this model is consistent with the observed sensitivity toward steric effects for substitution at C(2) but tolerance of a broad range of substitution on the indole nitrogen. IRC analysis indicates that transition state **D** leads to ylide **E**, the structure of which is shown in Figure 1c.

Computation was also used to consider the formation of an ylide intermediate via an electrophilic aromatic substitution-type mechanism. A transition state that does not possess oxocarbenium character was also located (see Supporting Information) and was found to be higher in energy than **D** by $\Delta\Delta E(\mathrm{ZPE})^{\ddagger}$ = 1.8 kcal/mol. In this higher energy transition state, the benzene ring of the indole is positioned above the ester functionality.

In our prior work on asymmetric cyclopropanation, we proposed that alignment of the carbenoid in the chiral crown cavity of Rh$_2$(*S*-PTTL)$_4$ leaves the *si*-face of the carbenoid more accessible for reactivity.[7a] Rh$_2$(*S*-NTTL)$_4$ also has a crown structure[10,11] (Figure 2a), and it is possible that a similar model for asymmetric induction may be in operation for the formation of ylide **E** (Figure 2b); aromatization and stereoretentive protonation of the C−Rh bond would then provide the indole product **F**. We consider that the conversion of **E** to **F** is stepwise, as computations suggest that an intramolecular 1,2-hydride shift for the conversion of **E** to **F** is not plausible ($\Delta E(\mathrm{ZPE})^{\ddagger}$ = 30.2 kcal/mol) at −78 °C. An alternative possibility is that asymmetry is induced via dynamic kinetic resolution of intermediate Rh−enolates (e.g., **G** and **G′** in Figure 2c) that are not configurationally stable.[15] In this scenario, the enantio-determining step would involve a dynamic equilibrium between **G** and **G′** that is faster than the rate of protonation (Figure 2c).

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To conclude, we have developed an enantioselective, Rh_2(*S*-NTTL)$_4$-catalyzed method for C−H functionalization of indoles by α-alkyl-α-diazoesters. From DFT calculations, a mechanism is proposed that involves a Rh−ylide intermediate with oxocarbenium character. Asymmetric induction may be explained by approach of the indole to the *si*-face of the Rh−carbene, with subsequent aromatization and stereoretentive protonation. Alternatively, asymmetric induction may occur via dynamic kinetic resolution of a rhodium enolate intermediate. Efforts to distinguish these mechanisms are ongoing.

■ ASSOCIATED CONTENT

Supporting Information. Full experimental details, ^{1}H and ^{13}C NMR spectra, stereochemical assignments, computational details, complete ref [1f], and crystallographic (CIF) data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Known substrate limitations: indole with ethyl α-diazobutanoate gave the product of N−H insertion in 29% yield and <1% ee; 6-(hydroxymethyl)-*N*-methylindole with ethyl α-diazo-5-methylhexanoate gave the product of O−H insertion in 41% yield and <1% ee; 1,2-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole with ethyl α-diazo-5-methylhexanoate gave the desired C−H functionalization product in 81% yield, but only 13% ee; 5-nitro-1,2-dimethylindole with ethyl α-diazobutanoate did not give any intermolecular products. (b) For the preparation of **16** and **17**, it was important to use only 1 equiv of diazoester. Enantioselectivity was lower and difficult to reproduce when 2 equiv of diazoester was used. Azine side products[7c] were formed when excess amounts of diazoesters were employed. We believe that the azine acts as a base that epimerizes **16** and **17**.

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