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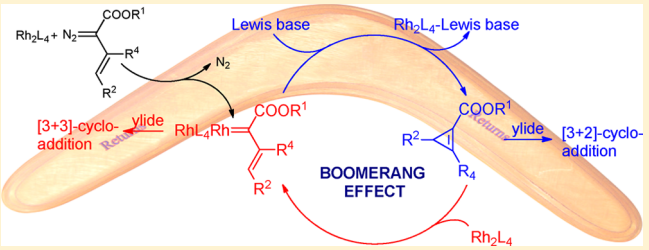
Catalytic Asymmetric Syntheses of Quinolizidines by Dirhodium-Catalyzed Dearomatization of Isoquinolinium/Pyridinium Methylides—The Role of Catalyst and Carbene Source

Xichen Xu, Peter Y. Zavalij, and Michael P. Doyle*

Department of Chemistry and Biochemistry, University of Maryland, College Park, 20742, United States

Supporting Information

ABSTRACT: Convenient access to highly enantioenriched substituted quinolizidines has been achieved by chiral dirhodium(II) carboxylate-catalyzed dearomatizing formal [3 + 3]-cycloaddition of isoquinolinium/pyridinium methylides and enol diazoacetates. Coordination of Lewis basic methylides to dirhodium(II) prompts the rearrangement of the enol-carbene that is bound to dirhodium to produce a donor–acceptor cyclopropene. The donor–acceptor cyclopropene is in equilibrium with the dirhodium-bound enol-carbene and undergoes both enantioselective [3 + 3]-cycloaddition from the dirhodium-bound enol-carbene and diastereoselective [3 + 2]-cycloaddition by uncatalyzed reaction of the cyclopropene with isoquinolinium or pyridinium methylides. Increasing the mol % of catalyst loading suppresses the [3 + 2]-cycloaddition pathway.

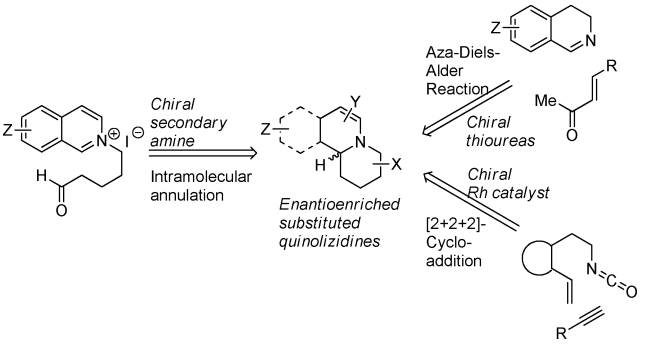


INTRODUCTION

Quinolizidines are isolated from myriad sources in nature, and they display diverse biological activities.[1] Among nitrogen-containing heterocyclic compounds, substituted quinolizidine alkaloids are exceptionally prominent,[1a] and some of them are lead compounds for the development of anticancer, anti-inflammatory, and cardiovascular drugs.[1b,c,d] Despite long-standing biological and synthetic interest in quinolizidines, methodologies for the synthesis of these valuable compounds have been limited. Asymmetric approaches to these systems have relied on either using reactants from the chiral pool,[1c,d] introducing chirality through the use of chiral auxiliaries,[2] or catalytic enantioselective approaches.[3−5] However, catalytic methods have been limited, and rhodium-catalyzed asymmetric [2 + 2 + 2]-cycloadditions of isocyanates,[3] catalytic asymmetric formal aza-hetero-Diels–Alder reactions[4] and one report of an organocatalytic enantioselective dearomatization of *N*-alkyl isoquinolinium salts (Scheme 1)[5] constitute the only current examples.

Although aromatic frameworks are capable of participating in reactions as electrophiles[6] or nucleophiles,[7] the development of catalytic asymmetric transformations directly engaging the aromatic π system has been achieved only recently.[8] We have been intrigued by asymmetric transformations involving catalytically generated metal carbene intermediates[9] that react with aromatic and heteroaromatic rings and furnish products ranging from electrophilic aromatic substitution (Friedel–Crafts reaction),[7] cyclopropanation and the subsequent Cope rearrangement (Büchner reaction),[10] and stable ylide forming reactions.[11] In these transformations, the electrophilic nature of metal carbenes dominates. We hypothesized that the catalytically generated chiral dirhodium carbene intermediates from

Scheme 1. Reaction Pathways to Enantioselective Synthesis of Substituted Quinolizidines



enol diazoacetates can be visualized as chiral metallo-1,3-dipole equivalents with their vinylogous position electrophilic and their metal carbene center nucleophilic, and this hypothesis has been recently verified in the highly enantioselective formal [3 + 3]-cycloaddition reaction of enol diazoacetates with aryl nitrones catalyzed by chiral dirhodium carboxylates.[9b] Intrigued by the potential uses of abundant and easily accessible nitrogen-containing heterocyclic rings as dipole acceptors, we reasoned that the formal [3 + 3]-cycloaddition strategy could be extended to stable and readily available isoquinolinium/pyridinium methylides with asymmetry introduced in the ring-closing dearomatization stage (Scheme 2).[12] Successful development of the asymmetric variant of this cycloaddition

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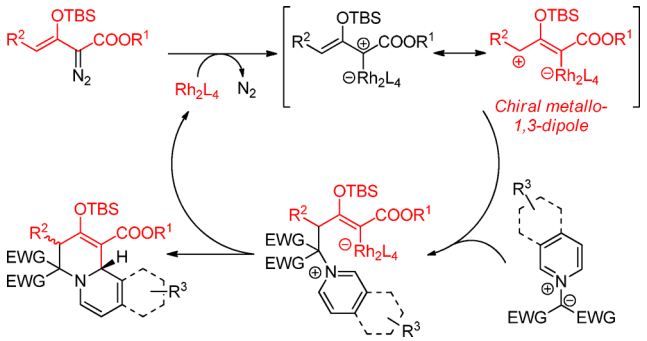
Scheme 2. Formal Enantioselective [3 + 3]-Cycloaddition of Metallo-1,3-dipoles with Isoquinolinium/Pyridinium Methylides



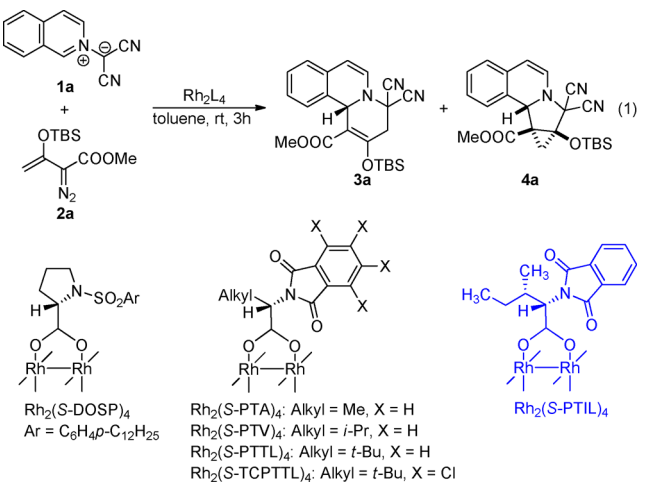
reaction would offer direct access to enantioenriched highly substituted quinolizidines that are amendable to further functionalization.[13] However, would the coordination of these Lewis basic methylides with the reaction catalyst inhibit the [3 + 3]-cycloaddition pathway and induce an alternative transformation?

Investigations of these systems not only revealed a highly enantioselective dearomatizing formal [3 + 3]-cycloaddition transformation of isoquinolinium/pyridinium methylides with enol diazacetates catalyzed by chiral dirhodium carboxylates in up to 96% ee, but they also provided evidence for competitive coordination-induced displacement of the dirhodium-bound enol-carbene as a donor–acceptor cyclopropene that either reforms the enol-carbene of dirhodium or undergos [3 + 2]-cycloaddition to form densely functionalized indolizidines with complete regioselectivity and diastereoselectivity.

RESULTS AND DISCUSSION

Optimization of reaction conditions aimed at maximizing the efficiency and selectivities for [3 + 3]-cycloaddition was initiated between isoquinolinium dicyanomethylide **1a** and enol diazoacetate **2a**. Performed in toluene by slowly adding a solution of enol diazoacetate **2a** to a mixture of partially soluble isoquinolinium dicyanomethylide **1a** and dirhodium catalyst, reactions occurred at room temperature (Table 1). When conducting the title reaction (eq 1) with excess **2a** in the presence of 1.0 mol % $Rh_2(Oct)_4$, complete consumption of the dicyanomethylide **1a** was achieved after 3 h. Two products were obtained as a 2.0:1 mixture in high isolated yield, and their structures were determined by spectroscopic analysis to be those from the anticipated (Scheme 2) [3 + 3]-cycloaddition (**3a**) and an unexpected diastereoselective [3 + 2]-cycloaddition of **1a**[14] with the donor–acceptor cyclopropene formed from **2a** by catalytic dinitrogen extrusion reaction (**4a**).[15] Use of $Rh_2(S\text{-DOSP})_4$ as the catalyst[16] formed **3a** and **4a** in a 1:4.2 product ratio (entry 2), but enantioselectivity for **3a** was very poor and for **4a** was not evident. Switching to Hashimoto's $Rh_2(S\text{-PTA})_4$ catalyst[17] resulted in a significant increase in enantioselectivity for the [3 + 3]-cycloaddition product **3a** (entry 3). The alkyl group of the Hashimoto's dirhodium catalysts impacted the enantiomeric excess for **3a** (entries 3–6), and optimal enantioselectivity for **3a** was achieved with previously unreported $Rh_2(S\text{-PTIL})_4$ whose ligand incorporates an additional chiral center. Lowering the reaction temperature to 0 °C slightly enhanced both the chemo- and enantioselectivity for **4a** but with low reaction yield (entry 7); and alternatively performing the reaction at 60 °C provided only

Table 1. Optimization of Reaction Conditions for Enantioselective Formal [3 + 3]-Cycloaddition of Isoquinolinium Dicyanomethylide 1a and Enol Diazoacetate 2a



entry[a]	catalyst (y mol %)	3a:4a[b,c]	yield (%)[d]	ee (%) of 3a[e]
1	$Rh_2(Oct)_4$ (1.0 mol %)	2.0:1	85	
2	$Rh_2(S\text{-DOSP})_4$ (1.0 mol %)	1:4.2	83	−20
3	$Rh_2(S\text{-PTA})_4$ (1.0 mol %)	3.7:1	81	49
4	$Rh_2(S\text{-PTV})_4$ (1.0 mol %)	1:1.7	79	90
5	$Rh_2(S\text{-PTTL})_4$ (1.0 mol %)	10:1	69	89
6	$Rh_2(S\text{-PTIL})_4$ (1.0 mol %)	1.6:1	83	93
7[f]	$Rh_2(S\text{-PTIL})_4$ (1.0 mol %)	1.9:1	49	94
8[g]	$Rh_2(S\text{-PTIL})_4$ (1.0 mol %)	1:2.1	70	90
9[h]	$Rh_2(S\text{-TCPTTL})_4$ (1.0 mol %)	1:>20	49	nd
10[h]	$Rh_2(tfa)_4$ (1.0 mol %)	1:>20	71	
11	$Rh_2(S\text{-PTIL})_4$ (0.5 mol %)	1:1.5	69	93
12	$Rh_2(S\text{-PTIL})_4$ (1.5 mol %)	4.3:1	82	93
13	$Rh_2(S\text{-PTIL})_4$ (2.0 mol %)	15:1	85	93
14	$Rh_2(S\text{-PTIL})_4$ (2.5 mol %)	>20:1	89	93
15	$Rh_2(S\text{-PTIL})_4$ (3.0 mol %)	>20:1	90	93
16	$Rh_2(S\text{-PTV})_4$ (3.0 mol %)	>20:1	88	90

[a]Reactions were performed at room temperature with 0.1 mmol of **1a** (1.0 equiv). An excess of **2a** (1.8 equiv) in 1.0 mL toluene was added to the reaction mixture via syringe pump over 1 h with continued stirring for another 2 h. [b]Ratios were determined by ^{1}H NMR analysis of reaction mixtures. Duplicate reactions show remarkable consistency in the **3a**:**4a** ratio. [c]The stereochemistry of **4a** was determined by ^{1}H NOE experiments. See SI for detail. [d]Yields reported are combined isolated yields of **3a** and **4a**. [e]Enantiomeric excesses were determined by chiral HPLC analysis. See SI for experimental detail. [f]Reaction performed at 0 °C. [g]Reaction performed at 60 °C. [h]Reaction was continued for 23 h after the completion of adding **2a**.

inferior selectivities (entry 8). Use of the more Lewis acidic $Rh_2(S\text{-TCPTTL})_4$,[18] however, reversed chemoselectivity with [3 + 2]-cycloaddition product **4a** as the sole reaction outcome (entry 9), and this reversal in chemoselectivity was mirrored in results from the use of Lewis acidic achiral $Rh_2(tfa)_4$ under otherwise identical conditions (entry 10).

Surprisingly, catalyst loading has a pronounced effect on chemoselectivity (**3a**:**4a**). For instance, reactions catalyzed by 0.5 mol % (entry 11) and 1.0 mol % (entry 6) of $Rh_2(S\text{-PTIL})_4$ at room temperature showed low selectivity for the formation of the [3 + 3]-cycloaddition product **3a**, and only a slight increase in the **3a**:**4a** ratio occurred when the temperature was lowered to 0 °C. However, significant increases in the ratio

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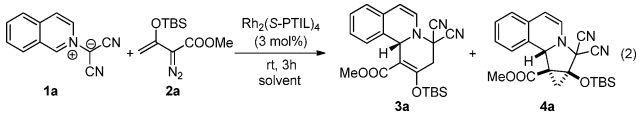
were observed with incremental increases in mol % catalyst so that at 2.0 mol % catalyst the ratio was 15.4 ± 0.4 (entry 13), and a further increase in catalyst loading to 2.5 then to 3.0 mol % led to the formation of **3a** as the sole reaction product [entries 14, 15, and 16 with $Rh_2(S\text{-PTV})_4$]. The excellent enantiomeric excesses obtained for **3a** were not at all affected by catalyst loading, which suggested that the formation of **3a** and **4a** was independent. The [3 + 2]-cycloaddition product **4a** was only obtained as a racemate.

Solvent strongly influenced both chemoselectivity and enantioselectivity. As is evident from the results reported in Table 2, reactions performed in chlorinated hydrocarbons

Table 2. Solvent Screening for the Enantioselective Catalytic Formal [3 + 3]-Cycloaddition Reaction of Isoquinolinium Dicyanomethylide 1a and Enol Diazoacetate 2a



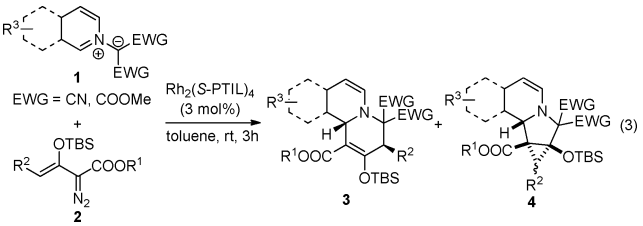
entry[a]	solvent	yield (%)[b]	3a:4a[c]	ee(%) of 3a[d]
1	CH_2Cl_2	71	2.4:1	72
2	$(CH_2Cl)_2$	59	4.8:1	80
3	$CHCl_3$	65	1.2:1	88
4	PhCl	79	1.6:1	90
5	*o*-xylene	77	>20:1	91
6	*p*-xylene	80	>20:1	80
7	PhF	74	>20:1	90
8	toluene	90	>20:1	93

[a]Reactions were performed on 0.1 mmol of **1a** (1.0 equiv), and an excess of **2a** (1.8 equiv) in 1.0 mL solvent was added to the reaction mixture via syringe pump over 1 h, and then reaction was continued with stirring for 2 h. [b]Ratios were determined by ^{1}H NMR analysis of reaction mixtures. [c]Reported yields are combined isolated yields of **3a** and **4a**. [d]Enantiomeric excesses were determined by chiral HPLC analysis.

(entries 1–4) gave significantly lower product control (**3a**:**4a**) and enantioselectivities for [3 + 3]-cycloaddition; aromatic solvents generally provided good chemoselectvities and high enantiocontrol (entries 5–7) except when chlorobenzene was used as solvent (entry 4). Toluene stood out as the optimal choice (entry 8).

The substrate scope of the enantioselective [3 + 3]-cycloaddition reaction was examined using the optimal conditions obtained with **1a** and **2a** (Table 1 entry 15), and these results are presented in Table 3. Product yields and enantioselectivities appear to be independent of the ester substituent of enol diazoacetate **2** (entries 1 and 2). The absolute configuration of **3b**, and others in this series by analogy, was unambiguously determined to be *S* through X-ray single crystal analysis (Figure 1). Enol diazoacetate **2c** with a methyl group instead of a hydrogen attached at the vinylogous position underwent the [3 + 3]-cycloaddition reaction with complete diastereocontrol (entry 3). Electronically disparate substituents on the isoquinolinium ring are well-tolerated (entries 4–7); consistently high reaction yields and high enantiomeric excesses were achieved. Furthermore, the more challenging[19] pyridinium dicyanomethylides (entries 8–10) participated in the [3 + 3]-cycloaddition transformation providing high yields and high enantiomeric excesses of quinolizidines that were comparable to those from the

Table 3. Substrate Scope for Enantioselective Dearomatizing Formal [3 + 3]-Cycloaddition



entry[a]	3	3:4[b]	yield (%)[c]	ee (%)[d]
1	**3a**	>20:1	90	93
2	**3b**	>20:1	89	93
3[e]	**3c**	>20:1	78	82
4	**3d**	>20:1	81	96
5	**3e**	>20:1	73	94
6	**3f**	>20:1	85	96
7	**3g**	1.7:1	63	95
8	**3h**	>20:1	85	87
9	**3i**	>20:1	88	86
10	**3j**	>20:1	76	74
11[f]	**3k**	>20:1	40	52

[a]Reactions were performed with 0.1 mmol of **1** (1.0 equiv) and an excess of **2** (1.8 equiv) in 1.0 mL toluene was added to the reaction mixture over 1 h, and then reacted for another 2 h. [b]Ratios were determined by ^{1}H NMR analyses of reaction mixtures. [c]Yields reported are combined isolated yields of **3** and **4**. [d]Enantiomeric excesses were determined by HPLC analyses on a chiral stationary phase. See SI for experimental details. [e]The stereochemistry of **3c** was determined by ^{1}H NOE experiments. See SI for details. [f]Reaction performed at 60 °C.

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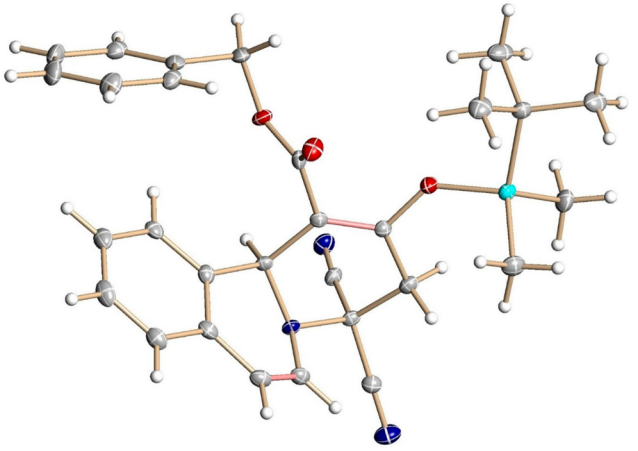
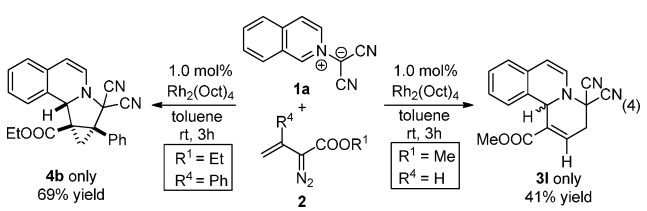


Figure 1. ORTEP view of benzyl (*S*)-2-(*tert*-butyldimethylsilyl)oxy-4,4-dicyano-4,11b-dihydro-3*H*-pyrido-[2,1-a]isoquinoline-1-carboxylate (**3b**). Ellipsoids are shown at 30% probability. CCDC 946885 contains supplementary crystallographic data for **3b**.

isoquinolinium systems. Interestingly, only a single regioisomer was obtained for 3-picolinium dicyanomethylide **1g**, although there were two potential reaction sites (entry 9), and the product obtained was the one from addition to the less sterically encumbered 6-position rather than to the 2-position.

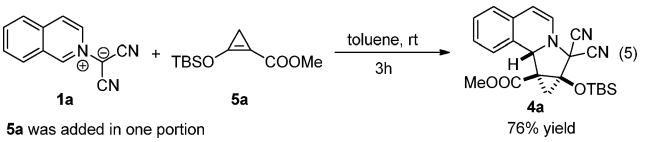
In contrast to the corresponding isoquinolium dicyanomethylides (**1**, EWG = CN), the dicarbomethoxy isoquinolinium methylide (**1i**, EWG = COOMe) was much less reactive toward dirhodium-catalyzed reaction with enol diazoacetate **2a**; reactions performed at room temperature reached only 30% completion in the normal 3 h reaction time. However, at 60 °C over the same time period the reaction reached full consumption of **1i**, and **3k** was isolated in moderate yield although with significantly lower enantiomeric excess (Table 2, entry 11) than from reaction with the corresponding dicyanomethylide **1a**. Overall, the dearomatizing [3 + 3]-cycloaddition methodology represents a general approach for the catalytic asymmetric functionalization of the dicyanomethylides of isoquinoline and pyridine. Although the dicarbomethoxy isoquinolinium methylide **1i** was much less reactive than **1a**, other heterocyclic ylides[14a,20] may have enhanced reactivity and selectivity for these cycloaddition reactions.

To probe the influence from alternate substituents (R^4) to the OTBS group on the vinyl group of **2**, combinations of vinyl diazoacetates **2** and methylide **1a** were subjected to $Rh_2(Oct)_4$ catalysis. Although such determinations have been conducted to compare product yields for individual transformations,[21] competitive reactions with **2** have not been reported. Whereas the reaction of **2a** (R^4 = OTBS) with **1a** gave a mixture of **3a** and **4a** (Table 1 entry 1); with R^4 = Ph the $Rh_2(Oct)_4$-catalyzed reaction afforded only the [3 + 2]-cycloaddition product **4b** (eq 4) and vinyldiazoacetate **2d** (R^4 = H) gave exclusive formation



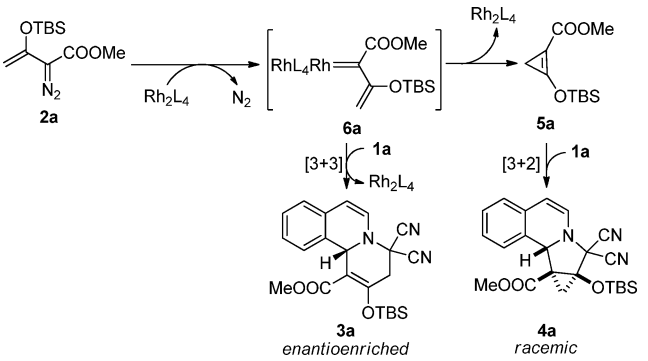
of the [3 + 3]-cycloaddition product **3l**. Similar to reaction outcomes with varying catalyst and reaction solvent, the influence of the vinyl substituent R^4 is substantial in its effect on reaction pathway.

The results from these experiments show a gradation in reactivity of the intermediate metal carbene toward either intermolecular [3 + 3]-cycloaddition with methylide **1a** to form **3** or isomerization to afford donor−acceptor cyclopropene **5**[15] that is susceptible to [3 + 2]-cycloaddition with **1a**. Since only racemic product was obtained with the diverse array of chiral catalysts that was employed (Table 1), the diastereoselective [3 + 2]-cycloaddition of **5** and **1** can be regarded to be a catalyst-free process. In sharp contrast, the high enantiocontrol in the [3 + 3]-cycloaddition process demonstrates its direct dependence on the dirhodium catalyst. In a separate experiment, treating the preformed and catalyst-free cyclopropene **5a** with isoquinolinium dicyanomethylide **1a** produced the [3 + 2]-cycloaddition product **4a** exclusively at room temperature (eq 5).



However, the mechanistic explanation in which the metal carbene formed from dirhodium carboxylate and the enol diazoacetate either reacts with methylide **1a** to produce the product from [3 + 3]-cycloaddition or dissociates the bound carbene with rearrangement in the form of the donor−acceptor cyclopropene **5** (Scheme 3) does not explain the dramatic

Scheme 3. Formation of Both [3 + 3]- and [3 + 2]-Cycloaddition Products are Dependent on Metal Carbene Intermediate 6



increase in the ratio of **3**:**4** with increasing mol % of catalyst loading (Table 1, entry 4,6, 11−16). The formation of both **3** and **4** have the same catalyst dependence in this scheme; both emanate from the metal carbene intermediate, and product formation for both involves reaction with **1**. Thus dependence of catalyst on product distribution suggests a more complex role for dirhodium in these transformations, and perhaps one that involves its coordination with methylide Lewis bases.

The coordination of the dirhodium carboxylate with an isoquinolinium methylide was assessed in toluene at room temperature. Unlike most of the methylides used in this study, 5-(*tert*-butyldimethylsilyloxy)isoquinolium dicyanomethylide **1e** displayed good solubility in most common organic solvents, and this feature enabled us to accurately determine the first coordination constant (K_1) of **1e** and $Rh_2(S\text{-PTIL})_4$. Coordination between $Rh_2(S\text{-PTIL})_4$ and dicyanomethylides

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1 was indicated by the intense color change of $Rh_2(S\text{-PTIL})_4$ from light green to deep red when they were mixed. A plot of the spectrum of the $Rh_2(S\text{-PTIL})_4$-containing solution as function of increasing amounts of methylide **1e** with minimal change in volume (Figure 2) shows a clear isosbestic point at

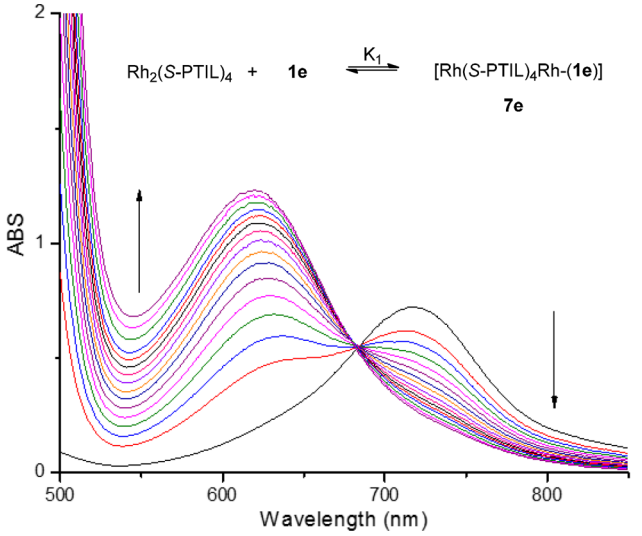
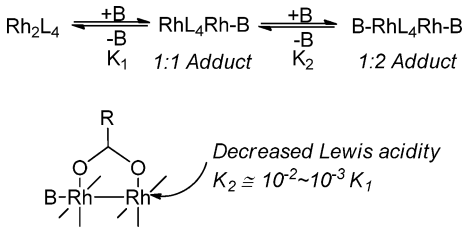


Figure 2. UV–vis titration curves and equilibrium constant K_1 for complex formation between **1e** and $Rh_2(S\text{-PTIL})_4$ in toluene at room temperature. $[Rh_2(S\text{-PTIL})_4]$ = 2.0 × 10^{-3} M; 0.17 equiv of **1e** [Relative to $Rh_2(S\text{-PTIL})_4$] was added in each increment. K_1 = 545 ± 14.

684 nm. The equilibrium constant for association between $Rh_2(S\text{-PTIL})_4$ and dicyanomethylides **1e** was determined to be 545 ± 14 by the methodology that we have previously employed,[22] which is a binding affinity comparable to that of the same dirhodium compound and acetonitrile (K_1 = 155 ± 2). Although coordination to rhodium through either the methanide carbon center of **1a** or through one of its nitrile nitrogens is possible, association through the nitrile nitrogen offers the lesser steric resistance.

Pioneering work by Drago[23] established that Lewis base coordination with Lewis acidic dirhodium carboxylates occurs at the axial positions to form 1:1 and 2:1 adducts with acetonitrile and with pyridine, and that the second coordination constant K_2 was at least two to 3 orders of magnitude lower than K_1 (Scheme 4). From this and a vast array of related investigations of the equilibrium processes of dirhodium carboxylates, the influence of one coordinated ligand on the association of a second ligand clearly established an inhibition for association;[24,25] but attempts to displace bound carbenes[26]

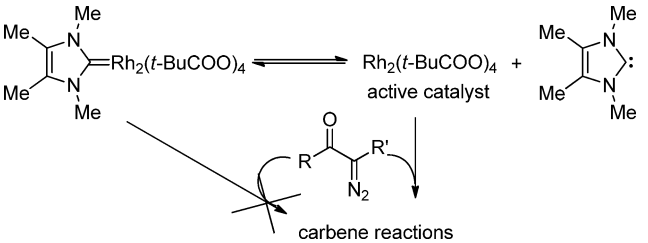
Scheme 4. Lewis Bases Occupy Axial Coordination Sites on Dirhodium Complexes



or demonstrate the influence of axial ligands on catalytic reactivity or selectivity[27] have not been successful.

In a recent attempt to determine if a bound ligand could influence a catalytic reaction, Padwa and co-workers synthesized a stable dirhodium carbene complex between an Arduengo carbene and dirhodium pivalate,[27a] but all endeavors to detect a unique reactivity or selectivity in cycloaddition or insertion reactions from diazocarbonyl compounds for this complex were unsuccessful. Identical catalytic reactivities and selectivities were obtained with the parent dirhodium catalyst, and the authors concluded that the ligated dirhodium carbene complex underwent dissociation of carbene ligand to release the active dirhodium catalyst (Scheme 5) that then participated in

Scheme 5. Stable Carbene on Dirhodium Undergoes Dissociation Prior to Reaction of Dirhodium with the Diazocarbonyl Compound

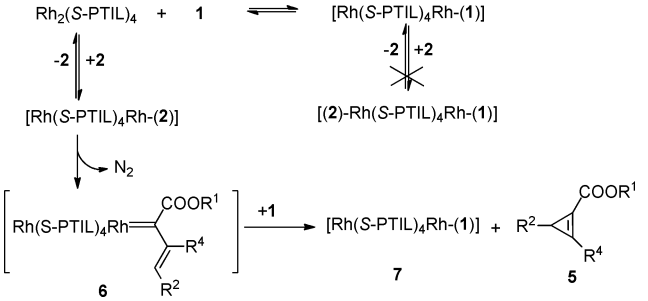


the catalytic metal carbene reactions. In contrast to this S_N1-like role for an axial carbene ligand, could the dependence of catalyst on product distribution in reactions of **1** with **2** be influenced by **1** as an axial ligand?

Recognizing that the catalyst in the reaction solution is in equilibrium with methylide **1**, addition of enol diazoacetate **2** could associate with the methylide-coordinated dirhodium catalyst or the catalyst that is free of **1**. The equilibrium constant for association between **1e** and $Rh_2(S\text{-PTIL})_4$ gives evidence of a complex, which is highly unlikely to associate the weakly coordinating diazo compound **2**. Instead, coordination with the catalyst that is free of methylide is most likely, and with dinitrogen extrusion this complex forms the metal carbene intermediate (Scheme 6). However, previous reports of the catalytic formation of donor–acceptor cyclopropenes **5** from enol diazoacetate **2** did not discuss how this product was formed.[15]

Two possible pathways exist for the displacement of the rhodium-bound carbene of **6** as cyclopropene **5**. One is the S_N1-like pathway that was demonstrated for the dirhodium carbene complex between an Arduengo carbene and dirhodium

Scheme 6. Reaction Pathway for the Formation of Cyclopropene 5



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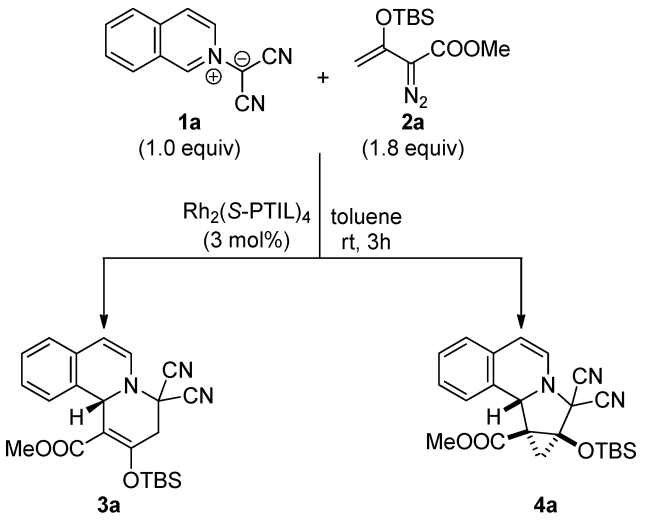
pivalate (Scheme 5). However, in this case, increasing the mol % of catalyst could not have influenced the ratio of [3 + 3]- to [3 + 2]-cycloaddition products, as has been explained (Scheme 3). However, if methylide **1** serves to induce formation of cyclopropene **5** in a through dirhodium S_N2'-like displacement reaction, the effect of increased dirhodium catalyst concentration will be to increase the concentration of **6** and thereby increase the rate for formation of [3 + 3]-cycloaddition product **3** relative to that of [3 + 2]-cycloaddition product **4** whose formation occurs subsequent to the formation of **5**. There are several lines of evidence that support this interpretation: (1) If the Lewis basic methylide **1** does assist the generation of cyclopropene **5** with concomitant release of a Lewis acid−base complex (Scheme 6), then this effect should be more pronounced in reactions catalyzed by more Lewis acidic dirhodium compounds (higher K_{eq}, lower concentration of ligand-free catalyst). As predicted, the [3 + 2]-cycloaddition pathway completely overrides the competing [3 + 3]-cycloaddition reaction when Rh_2(*S*-TCPTTL)$_4$ (Table 1, entry 9) or Rh_2(tfa)$_4$ (Table 1, entry 10) is used. (2) External Lewis base additives decrease the catalyst concentration and increase the production of cyclopropene **5**, thereby decreasing chemoselectivity for [3 + 3]-cycloaddition obtained from the reaction catalyzed by 3 mol % Rh_2(*S*-PTIL)$_4$ (Scheme 7). As

Scheme 7. Effect of Lewis Bases on Chemoselectivity



	Lewis base	
>95% (93% ee)	none (90% yield)	<5%
90% (93% ee)	3 equiv MeCN (69% yield)	10%
84% (93% ee)	5 equiv MeCN (51% yield)	16%
<5% (ee nd)	1 equiv Et_3N (13% yield)	>95%
<5% (ee nd)	1 equiv pyridine (<5% yield)	>95%

anticipated, more of the [3 + 2]-cycloaddition product **4a** is formed in reactions where CH_3CN or the more strongly coordinating Lewis base (Et_3N or pyridine) is present. That these additives do not influence the [3 + 3]-cycloaddition pathway is indicated by the observation that enantiomeric excesses of **3a** are not influenced by the presence of CH_3CN. Use of the stronger σ-donors—Et_3N or pyridine—completely shuts down the [3 + 3]-cycloaddition pathway. (3) The steady state approximation for formation of cyclopropene **5** in the competitive processes described in Scheme 3 suggests a direct relationship in the [**3**]/[**4**] ratio with [**1**] for the S_N1-like pathway, which is not observed, and no direct dependence on [**1**] for the S_N2'-like pathway.

Although the enantioselective [3 + 3]-cycloaddition and the diastereoselective [3 + 2]-cycloaddition reactions are linked through the intermediate rhodium carbene **6**, they are separated by the divergent outcomes from actions of methylide **1** on **6**. Lewis base additives do not participate in the enantioselective [3 + 3]-cycloaddition but they do induce rearrangement of rhodium carbene to generate cyclopropene **5**. Indeed, it is possible that the influence of at least some of the chlorinated solvents on reaction selectivity may arise from Lewis base displacement of cyclopropene **5** from the dirhodium carbene **6**.[28] However, when the bulky nitriles **3** or **4** were used as additives in the catalytic reactions, minimal impact on the product distribution was displayed.

Although the uncatalyzed reaction of methylide **1a** with donor−acceptor cyclopropene **5a**, formed by catalytic dinitrogen extrusion from enol diazoacetate **2a**, underwent [3 + 2]-cycloaddition exclusively, and this process adequately accounts for the formation of **4a**, the effect of increasing mol % catalyst on the relative yield of [3 + 3]-cycloaddition product **3a** (Table 1) coupled with the Lewis base promoted cyclopropene formation (Schemes 6 and 7) suggested that the role of the cyclopropene intermediate is more complex than what has been portrayed. Could cyclopropene **5a** form metal carbene **6** in what would be a reversal of the reaction that formed **5a**? Although cyclopropenes are known to be stoichiometric precursors to metal carbenes in selected cases,[29] only recently have reports emerged of catalytic reactions of cyclopropenes in metal carbene transformations.[30]

To test this hypothesis, we replaced enol diazoacetate **2a** in eq 1 with cyclopropene **5a**, generated with rhodium(II) acetate but separated from the catalyst, and performed reactions in the presence of variable mol % of Rh_2(*S*-PTIL)$_4$ under otherwise identical conditions. As anticipated, high enantiocontrol for the formation of the [3 + 3]-cycloaddition product **3a** was achieved; and this transformation and its enantioselectivity demonstrated the direct involvement of the chiral catalyst in the bond-forming steps. Chemoselectivities (**3a**:**4a**) directly correlated with the mol % of Rh_2(*S*-PTIL)$_4$ used, and the enantioselective [3 + 3]-cycloaddition product **3a** was obtained with greater than 95% selectivity when the catalyst loading was increased to 2 mol % (Scheme 8). Thus the outcomes of these reactions, including the enantioselectivity of **3a** and chemoselectivity for **3a**:**4a**, were identical and independent of the source of the carbene-forming reactant.

Considering the boomerang interconversion between the enol-TBS substituted chiral dirhodium carbene **6** and the donor−acceptor cyclopropene **5**, the relationship between the amount of catalyst and the ratio of products from [3 + 3]- and [3 + 2]-cycloaddition reactions now resembles the experimental observation (Scheme 9). If the interconversion between (**5** + Rh_2L_4) and **6** is rapid relative to cycloadditions, then the ratio **3**:**4** is directly related to the concentration of catalyst (Scheme 9). However, a plot of the ratio **3a**:**4a** versus mol % Rh_2(*S*-PTIL)$_4$ suggests a more complex exponential relationship with the catalyst that awaits further mechanistic definition.

Taking these findings into account, we now have a more complete rationale for the events that occur during the highly enantioselective dearomatizing [3 + 3]-cycloaddition reaction of enol diazoacetates and isoquinolinium or pyridinium methylides (Scheme 10). The central outcome is stereoselective cycloaddition that results from the vinylogous reaction

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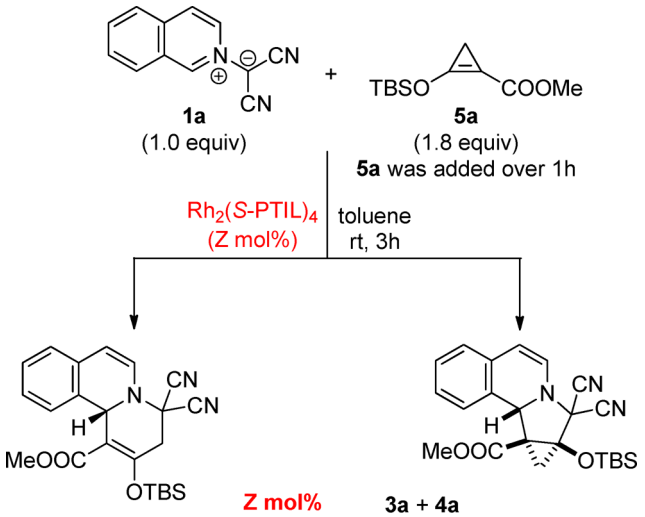
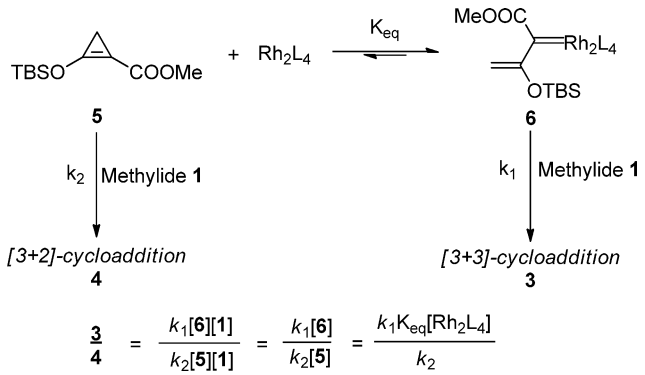
Scheme 8. Dependence of Product Distribution on Catalyst Loading with Cyclopropene 5a as the Metal Carbene Precursor



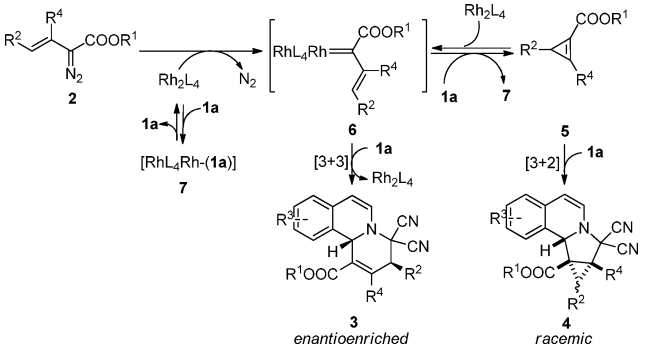
3a	Z mol% Rh_2(*S*-PTIL)$_4$	3a + 4a Yield	4a
<5% (nd)	0.0	61%	>95%
50% (93% ee)	0.5	66%	50%
75% (93% ee)	1.0	71%	25%
>95% (93% ee)	2.0	75%	<5%

Scheme 9. Relationship Between the Cycloaddition Product Ratio (3:4) and the Dirhodium Catalyst



$$\frac{3}{4} = \frac{k_1[6][1]}{k_2[5][1]} = \frac{k_1[6]}{k_2[5]} = \frac{k_1 K_{eq}[Rh_2L_4]}{k_2}$$

Scheme 10. Detailed General Mechanism for the Competing [3 + 3]- and [3 + 2]-Cycloaddition Reactions



of enol-TBS substituted chiral dirhodium carbene **6** with isoquinolinium or pyridinium methylides that is accompanied by ring closure to cycloaddition product **3** with displacement of the chiral catalyst. In competition with this process, the enol-TBS-substituted dirhodium carbene **6** forms donor–acceptor cyclopropene **5** that is proposed to occur by a through-rhodium–rhodium bond displacement by a Lewis base that includes isoquinolinium or pyridinium methylides. The dirhodium catalyst is in equilibrium with reactant isoquinolinium or pyridinium methylides that has the effect of lowering the turnover rate for [3 + 3]-cycloaddition. The decreased amount of catalyst allows direct [3 + 2]-cycloaddition of the donor–acceptor cyclopropene **5** with isoquinolinium or pyridinium methylides to form **4**. As with the isoquinolinium or pyridinium methylides that have multiple reaction pathways for product formation, so also does cyclopropene **5** which undergoes either [3 + 2]-cycloaddition with **1** or forms dirhodium carbene **6**. The net result is that the catalyst has ultimate control on the reaction pathway and reaction stereoselectivity.

The new processes uncovered in this study—S_N2' induced formation of donor–acceptor cyclopropene **5** and its boomerang equilibrium with the axial ligand-free dirhodium catalyst—are fundamental to understanding metal carbene reaction chemistry. The dirhodium carbene derived from enol diazoacetate **2** is uniquely capable of rearrangement to cyclopropene **5** with release of the dirhodium catalyst, and this reaction occurs in competition with vinylogous addition of methylides. Isoquinolinium and pyridinium methylides are relatively strong Lewis bases compared to acetonitrile which is a much stronger Lewis base than the reactant diazo compound, and their Lewis basicity prompts competing association with the dirhodium catalyst, vinylogous addition to the enol-TBS substituted dirhodium carbene **6**, and displacement of cyclopropene **5** from the enol-TBS substituted dirhodium carbene **6**. The further implications of these processes are under investigation.

In summary, we have disclosed a highly enantioselective dearomatizing [3 + 3]-cycloaddition reaction. A [3 + 2]-cycloaddition of isoquinolinium or pyridinium methylides with the cyclopropene derived from rhodium carbene competes with the [3 + 3]-cycloaddition reaction but can be turned on or off with a higher mol % of catalyst or increasing amount of Lewis base.

EXPERIMENTAL SECTION

Sample Procedure for the Preparation of Isoquinolinium/Pyridinium Dicyanomethylides. To a THF solution (2.0 mL) of 4-bromoisoquinoline (416 mg, 2.0 mmol) cooled to 0 °C, tetracyanoethylene oxide (298 mg, 2.1 mmol) dissolved in 2.0 mL THF was added dropwise over 10 min. The reaction solution was stirred at 0 °C for 12 h, during which time a yellow precipitate formed. After warming to room temperature, the reaction mixture was diluted with diethyl ether (10 mL), and the precipitate was filtered and washed with diethyl ether (5.0 mL). The resulting yellow solid was collected then dissolved in CH_2Cl_2. Diatomaceous earth (3.0 g) was added to the solution, and then solvent was removed under reduced pressure. The solid residue was loaded onto a silica gel column (with CH_2Cl_2 and ethyl acetate as eluents) to isolate 4-bromoisoquinolinium dicyanomethylide **1b** (234 mg, 0.86 mmol, 43% yield).

Preparation of Dirhodium(II) Tetrakis[*N*-Phthaloyl-(*S*,*S*)-*iso*-leucinate] Bis(ethyl acetate) Adduct [Rh_2(*S*-PTIL)$_4$(EtOAc)$_2$]. To a flame-dried, 50-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar, $Rh_2(OAc)_4$ (221 mg, 0.50 mmol), *N*-phthaloyl-(*S*,*S*)-*iso*-leucine (653 mg, 2.50 mmol) and chlorobenzene (25 mL) were added sequentially under a nitrogen atmosphere. The flask was fitted with a 10-mL Soxhlet extraction apparatus into which was placed a thimble containing 5 g of an oven-dried mixture of 2 parts sodium carbonate and 1 part of sand. The mixture was heated to reflux

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for 3 h and then cooled to room temperature. Solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (30 mL). The resulting solution was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (20 mL) and then dried over anhydrous Na_2SO_4. Filtration and subsequent solvent removal under reduced pressure furnished a green solid that was purified by column chromatography on silica gel (hexanes/EtOAc). The resulting green solid was dissolved in 5 mL ethyl acetate and 50 mL hexanes was then added to the solution. Green solids that formed after standing overnight at room temperature were collected by filtration, washed with hexanes (2 × 5 mL) and dried under high vacuum (0.1 Torr) at room temperature for 3 h to provide dirhodium(II) tetrakis[*N*-phthaloyl-(*S*,*S*)-*iso*-leucinate] bis(ethyl acetate) adduct [Rh_2(*S*-PTIL)$_4$(EtOAc)$_2$] (590 mg, 0.42 mmol, 83% yield).

Sample Procedure for the Enantioselective [3 + 3]-Cycloaddition of Isoquinolinium/Pyridinium Methylides 1 and Enol Diazoacetate 2. To a 10-mL flame-dried Schlenk flask containing a magnetic stirring bar, [Rh_2(*S*-PTIL)$_4$(EtOAc)$_2$] (4.2 mg, 0.0030 mmol), isoquinolinium dicyanomethylide **1a** (20 mg, 0.10 mmol) and 1.0 mL of toluene were added sequentially under a nitrogen atmosphere. Then the flask was capped by a rubber septum and the resulting solution was stirred at room temperature for 5 min before methyl 3-(*tert*-butyldimethylsilyl)oxy-2-diazobut-3-enoate **2a** (46 mg, 0.18 mmol) dissolved in 1.0 mL of toluene was added via syringe pump over 1 h. Stirring was continued at room temperature for 2 h after the completion of adding **2a**. Then the reaction solution was concentrated under reduced pressure and directly loaded onto a silica gel column (with 1:1 of CH_2Cl_2:hexanes as eluents) to isolate methyl (*S*)-2-(*tert*-butyldimethylsilyl)oxy-4,4-dicyano-4,11b-dihydro-3*H*-pyrido[2,1-a]isoquinoline-1-carboxylate **3a** (38 mg, 0.090 mmol, 90% yield). HPLC analysis of the enantioselective [3 + 3]-cycloaddition product **3a** on a chiral stationary phase indicated an enantiomeric excess of 93% [Chiralpak OD-H; flow rate: 1.0 mL/min; hexanes/i-PrOH: 95:5; 254 nm; tR (minor) = 5.5 min; tR (major) = 6.2 min].

Sample Procedure for the Enantioselective [3 + 3]-Cycloaddition of Isoquinolinium/Pyridinium Methylides 1 and Enol Diazoacetate 2 in the Presence of a Lewis Base. To a 10-mL flame-dried Schlenk flask containing a magnetic stirring bar, [Rh_2(*S*-PTIL)$_4$(EtOAc)$_2$] (4.2 mg, 0.0030 mmol), isoquinolinium dicyanomethylide **1a** (20 mg, 0.10 mmol), 1.0 mL of toluene and CH_3CN (12 mg, 0.30 mmol) were added sequentially under a nitrogen atmosphere. Then the flask was capped by a rubber septum and the resulting solution was stirred at room temperature for 5 min before methyl 3-(*tert*-butyldimethylsilyl)oxy-2-diazobut-3-enoate **2a** (46 mg, 0.18 mmol) dissolved in 1.0 mL of toluene was added via syringe pump over 1 h. Stirring was continued at room temperature for 2 h after the completion of adding **2a**. Then the reaction solution was concentrated under reduced pressure. The residue was dissolved in $CDCl_3$ to determine the ratio of **3a**:**4a** by ^{1}H NMR spectroscopy. Then the solution was directly loaded onto a silica gel column (with 1:1 of CH_2Cl_2:hexanes as eluents) to isolate methyl (*S*)-2-(*tert*-butyldimethylsilyl)oxy-4,4-dicyano-4,11b-dihydro-3*H*-pyrido[2,1-a]-isoquinoline-1-carboxylate **3a** (26 mg, 0.062 mmol, 62% yield). HPLC analysis of **3a** on chiral stationary phase showed an enantiomeric excess of 93%.

Procedure for the Generation of Methyl 2-(*tert*-Butyldimethylsilyl)oxy-cycloprop-1-enecarboxylate 5a in Toluene from Enol Diazoacetate 2a by $Rh_2(OAc)_4$-catalyzed Dinitrogen Extrusion Reaction. To a flame-dried vial equipped with a magnetic stirring bar, $Rh_2(OAc)_4$ (0.9 mg, 0.0020 mmol) and 0.75 mL toluene were added sequentially under a nitrogen atmosphere and then capped with a rubber septum. The solution was stirred at room temperature while methyl 3-(*tert*-butyldimethylsilyl)oxy-2-diazobut-3-enoate **2a** (46 mg, 0.18 mmol) was added dropwise over 1 min. Rapid evolution of nitrogen occurred, and the yellow color of **2a** disappeared within 5 min. Complete consumption of enol diazoacetate **2a** and the generation of donor−acceptor cyclopropene **5a** were verified by ^{1}H NMR spectroscopy by the disappearance of the two vinyl protons [δ (ppm): 5.02 (d, J = 2.1 Hz, 1H), 4.27 (d, J = 2.1 Hz, 1H)] on enol diazoacetate **2a** and the appearance of the methylene protons [δ (ppm): 1.88 (s, 2H)] from cyclopropene **5a**. The solution was filtered through a short pad (~1 cm) of BAKERBOND-CN silica (40 μm Prep LC packing) to remove the dirhodium catalyst and the silica pad was washed with 0.25 mL toluene. The combined filtrates containing methyl 2-(*tert*-butyldimethylsilyl)oxy-cycloprop-1-enecarboxylate **5a** were used directly in the subsequent reactions.

Sample Procedure for the Diastereoselective [3 + 2]-Cycloaddition of Isoquinolinium/Pyridinium Methylides 1 and cyclopropene 5. To the prepared toluene solution of methyl 2-(*tert*-butyldimethylsilyl)oxy-cycloprop-1-enecarboxylate **5a** at room temperature, isoquinolinium dicyanomethylide **1a** (20 mg, 0.10 mmol) was added as a solid under a nitrogen atmosphere. The resulting suspension was stirred at room temperature for 3 h during which time the mixture gradually became a homogeneous solution. The solution was then concentrated under reduced pressure and directly loaded onto a silica gel column (with 1:1 of CH_2Cl_2:hexanes as eluents) to isolate methyl (8a*SR*,9a*SR*,9b*SR*)-8a-(*tert*-butyldimethylsilyl)oxy-8,8-dicyano-8a,9,9a,9b-tetrahydro-8*H*-cyclopropa[3,4]pyrrolo[2,1-a]-isoquinoline-9a-carboxylate **4a** (32 mg, 0.076 mmol, 76% yield).

Sample Procedure for the Enantioselective [3 + 3]-Cycloaddition of Isoquinolinium/Pyridinium Methylides 1 and cyclopropene 5. To a 10-mL flame-dried Schlenk flask containing a magnetic stirring bar, [Rh_2(*S*-PTIL)$_4$(EtOAc)$_2$] (2.8 mg, 0.0020 mmol), isoquinolinium dicyanomethylide **1a** (20 mg, 0.10 mmol) and 1.0 mL of toluene were added sequentially under a nitrogen atmosphere. Then the flask was capped by a rubber septum and the resulting solution was stirred at room temperature. The prepared toluene solution of methyl 2-(*tert*-butyldimethylsilyl)oxy-cycloprop-1-enecarboxylate **5a** was added to the stirring mixture of [Rh_2(*S*-PTIL)$_4$(EtOAc)$_2$] and isoquinoline dicyanomethylide **1a** over 1 h via syringe pump. Stirring was continued at room temperature for 2 h after the completion of adding **2a**. Then the reaction solution was concentrated under reduced pressure and directly loaded onto a silica gel column (with 1:1 of CH_2Cl_2:hexanes as eluents) to isolate methyl (*S*)-2-(*tert*-butyldimethylsilyl)oxy-4,4-dicyano-4,11b-dihydro-3*H*-pyrido[2,1-a]isoquinoline-1-carboxylate **3a** (32 mg, 0.075 mmol, 75% yield). HPLC analysis of the enantioselective [3 + 3]-cycloaddition product **3a** on chiral stationary phase showed an enantiomeric excess of 93%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization data, chiral HPLC analyses, and crystal structures for **3b**, **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

mdoyle3@umd.edu

Notes

The authors declare no competing financial interest.

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