Asymmetric Catalysis

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Highly Enantioselective Dearomatizing Formal [3+3] Cycloaddition Reactions of *N*-Acyliminopyridinium Ylides with Electrophilic Enol Carbene Intermediates**

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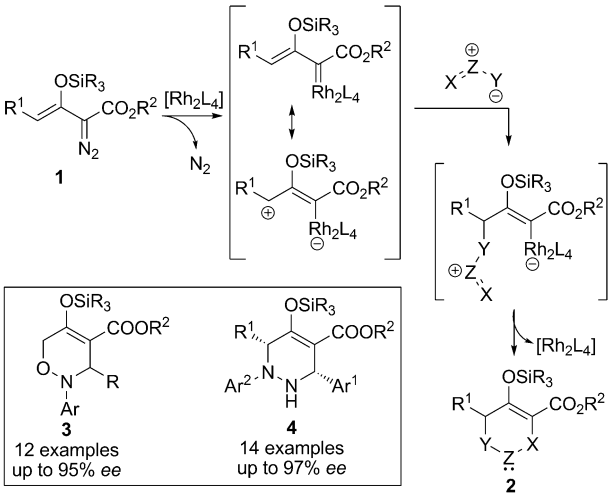
Heterocyclic compounds are widely distributed in nature,[1] and their core structures are present in a vast array of pharmaceuticals.[2] Although extensive efforts have concentrated on their syntheses,[3] including asymmetric catalytic processes,[4] the demand for greater structural diversity continues to be of intense interest.[5] In particular, there is increasing interest in the asymmetric synthesis of dihydropyridine, dihydroquinoline, dihydroisoquinoline, and related heterocycles, which are core structures in natural products and other bioactive molecules.[4a–f] However, the asymmetric synthesis of heterocyclic structures with more than one nitrogen atom is rare.[6–8]

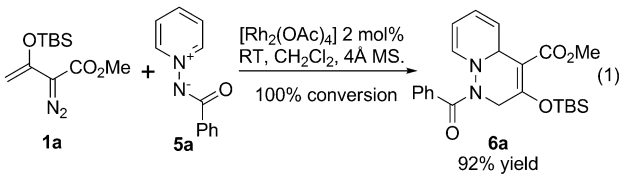
The use of *N*-iminoquinolinium ylides for the asymmetric construction of dihydroquinoline derivatives by a [3+3] cycloaddition with 1,1-cyclopropane diesters, originally reported by Charette and co-workers for the non-asymmetric version,[7e] was recently reported.[4a] Good yields and high enantiocontrol were achieved in this kinetic resolution, but high catalyst loadings of nickel(II) perchlorate and a chiral In-bis(oxazoline) ligand were required. We have been investigating the dirhodium-catalyzed 1,3-dipolar [3+3] cycloaddition with enol diazoacetates **1**.[9,10] The metal/enol carbene intermediates generated by dinitrogen extrusion have electrophilic character at both the carbene and vinylogous positions, with preferential reaction occurring at the vinylogous position (Scheme 1). Could these dipolar intermediates be effective for the asymmetric construction of dihydroquinoline derivatives with *N*-iminoquinolinium ylides? Prior efforts have shown that enol carbene intermediates undergo [3+3] cycloaddition reactions with nitrones to form 3,6-dihydro-1,2-oxazines **3**[9a] and with hydrazones to form tetrahydropyridazine derivatives **4**,[9c] each by a stepwise process initiated by nucleophilic reaction at the vinylogous position, which occurs with high enantiocontrol. Unlike cycloaddition reactions with nitrones and hydrazones, however, reactions there is an energy barrier to cycloaddition with the required dearomatization with *N*-iminoquinolinium ylides, and for this reason it is perhaps not surprising that cycloaddition reactions with *N*-iminopyridinium ylides have not yet been reported. We report herein that *N*-iminopyridinium ylides undergo efficient and highly enantioselective [3+3] cycloaddition reactions with



Scheme 1. Formal [3+3] cycloaddition reactions catalyzed by a vinylogous dirhodium enol carbene.

enol diazoacetates in the presence of a chiral dirhodium catalyst.

Pyridine-*N*-aminidines **5a** (*N*-acyliminopyridinium ylides)[4a,11] are stable but reactive dipolar species. Treatment of **5a** with enol diazoacetate **1a** in the presence of a catalytic amount of rhodium(II) acetate in dichloromethane at room temperature produced the dearomatized bicyclic tetrahydropyridazine derivative **6a** (92% isolated yield) in one step [Eq. (1), TBS = *tert*-butyldimethylsilyl]. This transformation



is a more direct and convenient way to the tetrahydropyridazine derivatives compared to previous two-step one-pot methods from *N*-arylhydrazones and **1a**.[9c] Furthermore, the bicyclic tetrahydropyridazine products that are obtained (**6**) offer more functional diversity than **4**.

On the basis of our previous studies,[9a,c] Hashimoto's dirhodium carboxylate catalysts were considered to have the reactivity and selectivity suitable for the [3+3] cycloaddition to be carried out with high enantioselectivity;[12] however, although 100% conversion was obtained when the reaction

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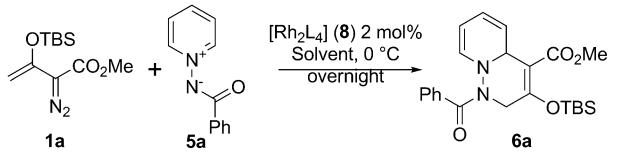
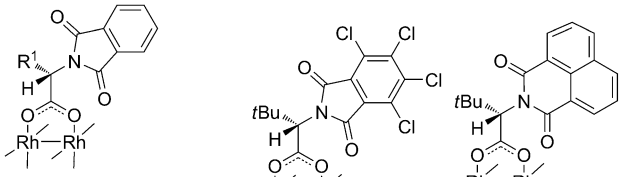
was catalyzed by $[Rh_2(S\text{-PTA})_4]$ in CH_2Cl_2, only 5% *ee* was detected (Table 1, entry 1).[13] The enantiomeric excess was increased to 45% by switching the solvent from CH_2Cl_2 to methyl *tert*-butyl ether (TBME) or toluene, with 71% and

Table 1: Optimization of conditions for the enantioselective formal [3+3] cycloaddition of enol diazoacetate **1a** with **5a**.[a]



Entry	$[Rh_2L_4]$ (**8**)	Solvent	Conv. [%][b]	*ee* [%][c]
1	$[Rh_2(S\text{-PTA})_4]$ (**8a**)	CH_2Cl_2	100	5
2	$[Rh_2(S\text{-PTA})_4]$ (**8a**)	TBME	71	50
3	$[Rh_2(S\text{-PTA})_4]$ (**8a**)	toluene	100	50
4	$[Rh_2(S\text{-PTL})_4]$ (**8b**)	toluene	100	50
5	$[Rh_2(S\text{-PTTL})_4]$ (**8c**)	toluene	100	83
6	$[Rh_2(S\text{-PTPA})_4]$ (**8d**)	toluene	100	51
7	$[Rh_2(S\text{-TCPTTL})_4]$ (**8f**)	toluene	100	71
8	$[Rh_2(S\text{-NTTL})_4]$ (**8g**)	toluene	100	71
9	$[Rh_2(S\text{-PTTL})_4]$ (**8c**)	fluorobenzene	91 (85)[d]	90
10	$[Rh_2(S\text{-PTTL})_4]$ (**8c**)	chlorobenzene	95 (81)[d]	89
11	$[Rh_2(S\text{-PTTL})_4]$ (**8c**)	*o*-xylene	100 (79)[d]	85
12	$[Rh_2(S\text{-PTTL})_4]$ (**8c**)	$CHCl_3$	26	93
13	$[Rh_2(S\text{-PTAD})_4]$ (**8e**)	toluene	100 (88)[d]	89
14	$[Rh_2(S\text{-PTAD})_4]$ (**8e**)	fluorobenzene	100 (86)[d]	89

[a] Reactions were carried out on a 0.2 mmol scale: **1a** (0.24 mmol), **5a** (0.20 mmol), and 4 Å MS (50 mg) in 2.0 mL of the indicated solvent with the corresponding dirhodium catalyst (2.0 mol%) at 0°C. [b] Determined from the ^{1}H NMR spectra of the reaction mixtures based on the limiting reagent **5a**. [c] Determined by HPLC analysis using IA columns with a chiral stationary phase (hexanes/*i*PrOH = 94:6, 254 nm, 1.0 mL min^{-1}, $t1 = 8.7$, $t2 = 12.4$). [d] Yield of isolated product **6a** based on the limiting reagent **5a**.



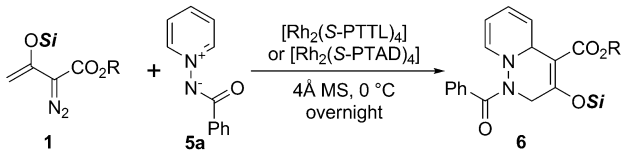
R^1 = Me, $[Rh_2(S\text{-PTA})_4]$ (**8a**)
R^1 = *i*Bu, $[Rh_2(S\text{-PTL})_4]$ (**8b**)
R^1 = *t*Bu, $[Rh_2(S\text{-PTTL})_4]$ (**8c**)
R^1 = Bn, $[Rh_2(S\text{-PTPA})_4]$ (**8d**)
R^1 = 1-adamantyl, $[Rh_2(S\text{-PTAD})_4]$ (**8e**)

$[Rh_2(S\text{-TCPTTL})_4]$ (**8f**) $[Rh_2(S\text{-NTTL})_4]$ (**8g**)

100% conversion, respectively (entries 2 and 3). Catalyst screening showed that increasing the steric demand of the ligands on the rhodium center resulted in higher enantioselectivity (entries 3–8), which was opposite to previous results with reactions of enol diazoacetates and nitrones[9a] or hydrazones[9c] (Scheme 1), in which the less sterically encumbered catalyst gave higher reactivity and selectivity. Further optimization of the solvents (entries 9–12) gave **6a** in up to 93% *ee* in chloroform, but there was only 26% conversion (entry 12). The combination having the highest conversion/yield and enantioselectivity was obtained when the reaction was catalyzed by $[Rh_2(S\text{-PTTL})_4]$[14] in fluorobenzene at 0°C, with the product isolated in 85% yield and 90% *ee* (entry 9). Similar results were obtained with $[Rh_2(S\text{-PTAD})_4]$[15] in fluorobenzene or toluene (entries 13 and 14).

A variety of enol diazoacetates **1** were examined under the optimized reaction conditions. As shown in Table 2, except for benzyl enol diazoacetate **1e** (entry 5, 85% yield 77% *ee*), all of the TBS- or TIPS-protected enol diazoacetates

Table 2: Enantioselective formal [3+3] cycloadditon of enol diazoacetates **1** with **5a**.[a]



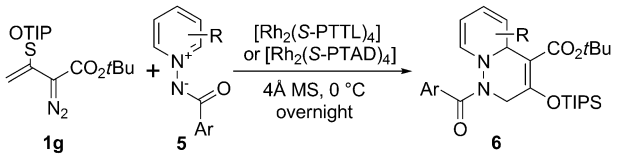
Entry	Me/***Si*** (**1**)	Cond.	**6**	Yield [%][b]	*ee* [%][c]
1	Me/TBS (**1a**)	A	**6a**	85	90
2	*i*Pr/TBS (**1b**)	D	**6b**	87	90
3	Cy/TBS (**1c**)	D	**6c**	83	91
4	*t*Bu/TBS (**1d**)	D	**6d**	91	94
5	Bn/TBS (**1e**)	D	**6e**	85	77
6	Me/TIPS (**1f**)	D	**6f**	91	90
7	*t*Bu/TIPS (**1g**)	D	**6g**	75	95
8	*t*Bu/TIPS (**1g**)	A	**6g**	81	95
9	*t*Bu/TIPS (**1g**)	C	**6g**	78	94

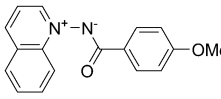
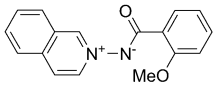
[a] Reactions were carried out on a 0.2 mmol scale: **1** (0.24 mmol), **5a** (0.20 mmol), and 4 Å MS (50 mg) in 2.0 mL solvent with dirhodium catalyst (2.0 mol%). Conditions A: catalyzed by $[Rh_2(S\text{-PTTL})_4]$ in fluorobenzene; conditions B: catalyzed by $[Rh_2(S\text{-PTTL})_4]$ in toluene; conditions C: catalyzed by $[Rh_2(S\text{-PTAD})_4]$ in fluorobenzene; conditions D: catalyzed by $[Rh_2(S\text{-PTAD})_4]$ in toluene. [b] Yield of isolated **6** based on the limiting reagent **5a**. [c] Determined by HPLC analysis on a chiral stationary phase, see the Supporting Information for details. Cy = cyclohexyl, TIPS = triisopropylsilyl.

gave the corresponding bicyclic tetrahydropyridazines **6** in high yield and high to excellent enantioselectivity (entries 1–4 and 6–7, > 75% yield, 90–95% *ee*). It is worth mentioning that the enantioselectivity increased as the steric demand of the enol diazoacetates **1** increased, but the product yields were not affected. In our previously reported reactions of enol diazoacetates with steric bulky hydrazones, the yields of the corresponding tetrahydropyridazine derivatives dropped dramatically with increasing steric demand.[9c] For the TIPS-protected *tert*-butyl diazoacetate **1g**, conditions A, C, or D gave similar enantioselectivities (entries 7–9), while conditions A afforded higher yields.

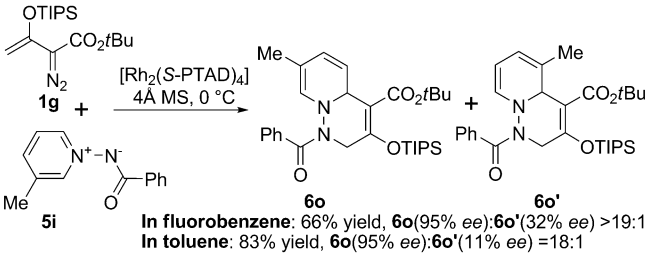
The reaction scope was extended to substituted *N*-acyliminopyridinium ylides (Table 3). The steric and electronic properties of the substituents on the phenyl group had a slight influence on the reactivity or selectivity (Table 3, entries 1–5), and the reaction could be carried out on a 1.0 mmol scale with 96% *ee* (entry 4). Notably, quinoline and isoquinoline derivatives were both well-tolerated in this [3+3] cycloaddition reaction and gave tricyclic tetrahydropyridazine derivatives in high yields and 97% *ee* and 96% *ee*, respectively (entries 6 and 7). Furthermore, high regioselectivity (> 19:1) was found when a 3-methyl group was introduced on the pyridinium ring (Scheme 2, **6o** and **6o′**),[16] with the major isomer obtained with 95% *ee* and

Table 3: Enantioselective formal [3+3] cycloaddition of enol diazoacetates **1g** with **5**.[a]



Entry	5		Cond.	6	Yield [%][b]	*ee* [%][c]
1	R = H, Ar = 4-MeOC$_6$H$_4$ (**5b**)		C	**6h**	87	95
2	R = H, Ar = 3-MeOC$_6$H$_4$ (**5c**)		C	**6i**	89	97
3	R = H, Ar = 2-MeOC$_6$H$_4$ (**5d**)		C	**6j**	80	98
4	R = H, Ar = 4-BrC$_6$H$_4$ (**5e**)		A	**6k**	77 (61)[d]	95 (96)[d]
5	R = H, Ar = 2-ClC$_6$H$_4$ (**5f**)		C	**6l**	88	98
6		(**5g**)	A B	**6m**	63 72	94 96
7		(**5h**)	D	**6n**	71	97

[a] Reactions were carried out on a 0.2 mmol scale: **1g** (0.24 mmol), **5** (0.20 mmol), and 4 Å MS (50 mg) in 2.0 mL solvent with dirhodium catalyst (2.0 mol%). Conditions A: catalyzed by [Rh$_2$(*S*-PTTL)$_4$] in fluorobenzene; conditions B: catalyzed by [Rh$_2$(*S*-PTTL)$_4$] in toluene; conditions C: catalyzed by [Rh$_2$(*S*-PTAD)$_4$] in fluorobenzene; conditions D: catalyzed by [Rh$_2$(*S*-PTAD)$_4$] in toluene. [b] Yield of isolated **6** based on the limiting reagent **5**. [c] Determined by HPLC on a chiral stationary phase, see the Supporting Information for details. [d] Reaction carried out on a 1.0 mmol scale.



Scheme 2. Highly regioselective and enantioselective formal [3+3] cycloaddition of enol diazoacetate **1g** with **5i**.

the minor isomer with 32% *ee*. These results indicated that the dirhodium catalyst is still associated with the substrate during the ring-closing step, and this association determines which of the two positions is the preferential reaction site when catalyzed by chiral dirhodium catalyst.[17]

The *S* configuration of the generated stereogenic center in bicyclic tetrahydropyridazine derivatives was confirmed by single-crystal X-ray diffraction analysis of **6i**,[18] and the configurations of other compounds were tentatively assigned by analogy (Figure 1). As is evident from this determination, the *S*-configured catalyst yields the *S*-configured cycloaddition product. The generated bicyclic tetrahydropyridazine derivatives have multiple functional groups, including an ester, an ether, an acyl, and a diene generated by dearomatization of the *N*-acyliminopyridinium ylide. A one-pot reaction with *N*-phenylmaleimide gave the polycyclic product **7** in 77% yield with 2:1 *endo*/*exo* selectivity, with the two diastereoisomers having the same enantioselectivity as in the case of **6g** (Scheme 3).

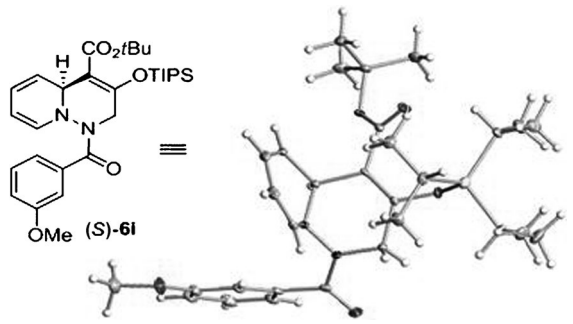
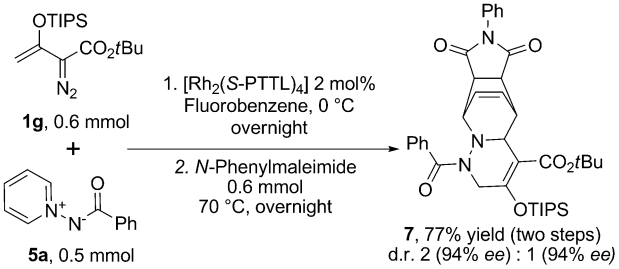


Figure 1. An *S* configuration of **6i** is produced when [Rh$_2$(*S*-PTAD)$_4$] is used as the catalyst.

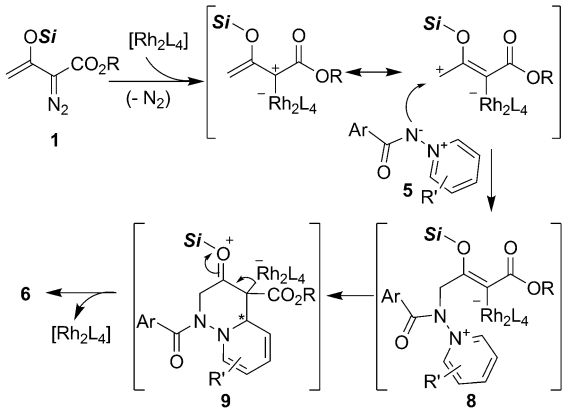


Scheme 3. Sequential one-pot [3+3]/[4+2] cycloaddition reactions.

In summary, we have developed a direct formal [3+3] cycloaddition that provides an effective access to bicyclic and tricyclic 1,2,3,6-tetrahydropyridazine derivatives starting from enol diazoacetates and *N*-acyliminopyridinium ylide. The good to high overall yields, high regioselectivities, and excellent enantioselectivities observed are controlled by the catalysts and conditions. The sequence of reactions is triggered by Rh(II)-catalyzed dinitrogen extrusion followed by vinylogous addition with *N*-acyliminopyridinium ylides. Intramolecular asymmetric addition of pyridinium ylide to the catalyst-activated vinyl ether group of **8** forms the [3+3] cycloaddition product **6** (Scheme 4). The generated 1,2,3,6-tetrahydropyridazine product can be transformed to polycyclic skeletons through a [4+2] cycloaddition without sacrificing the enantiomeric excess. Further expansion of the cycloaddition with electrophilic enol carbene intermediates applied broadly is being pursued.

Experimental Section

Conditions A: *N*-acyliminopyridinium ylide **5** (0.20 mmol), 4 Å molecular sieves (50 mg), [Rh$_2$(*S*-PTTL)$_4$] (2.0 mol%), and fluorobenzene (1.0 mL) was cooled to 0 °C in an oven-dried flask containing a magnetic stirring bar. A solution of the enol diazoacetate **1** (0.24 mmol) in fluorobenzene (0.5 mL) was added over 1 h by



Scheme 4. Proposed reaction pathway for the [3+3] cycloaddition.

syringe pump and the reaction mixture was stirred overnight. Pure tetrahydropyridazine derivatives **6** were obtained in high yield with high enantioselectivity by column chromatography on silica gel (eluent: hexanes/EtOAc = 100:0 to 90:10).

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[18] See the supporting information for details. CCDC 923840 (**6i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

