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

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Abstract

A effective dearomatizing formal [3+3]-cycloaddition reaction triggered by Rh(II)-catalyzed dinitrogen extrusion of enoldiazoacetates followed by vinylogous addition of metal enolcarbenes to *N*-acyliminopyridinium ylides that produces highly substituted 1,2,3,6-tetrahydropyridazines in up to 98% *ee* and in high yield has been developed.

Keywords

asymmetric catalysis; cycloaddition; diazo compounds; heterocycles; enantioselectivity

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 been 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 are increasing efforts for asymmetric syntheses of dihydropyridine, dihydroquinoline, dihydroisoquinoline and related heterocycles that are core structures in natural products and other bioactive molecules.^[4a–4f] However, asymmetric syntheses of heterocyclic structures with more than one nitrogen-atom are 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 for the non-asymmetric version,^[7e] has recently been communicated.^[4a] Good yields and high enantiocontrol were achieved in this kinetic resolution, but high catalyst loadings of nickel(II) perchlorate and the chiral In-Box ligand were required. We have been investigating the dirhodium-catalyzed 1,3-dipolar [3+3]-cycloaddition with enol-diazoacetates **1**^[9,10] whose metal enolcarbene intermediates, generated by dinitrogen

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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 enolcarbene intermediates underwent [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 that occurs with high enantiocontrol. Unlike cycloaddition reactions with nitrones and hydrazones, however, reactions with *N*-iminoquinolinium ylides afford a barrier to cycloaddition with the required dearomatization, and for this reason it is perhaps not surprising that cycloaddition reactions with *N*-iminopyridinium ylides have not yet been reported. We wish to report that *N*-iminopyridinium ylides undergo efficient and highly enantioselective [3+3]-cycloaddition reactions in chiral dirhodium-catalyzed reactions with enol diazoacetates.

Pyridine-*N*-aminidines **5a** (*N*-acyliminopyridinium ylides)^[4a,11] are stable but reactive dipolar species. Treatment of **5a** with enoldiazoacetate **1a** in the presence of a catalytic amount of rhodium(II) acetate in dichloromethane (DCM) at room temperature produced the dearomatized bicyclic tetrahydropyridazine derivative **6a** (92% isolated yield) in one step (Eq 1). This transformation is a more direct and convenient way to the tetrahydropyridazine derivatives compared to previous two-step one-pot methodology from *N*-arylhydrazones and **1a**,^[9c] and the bicyclic tetrahydropyridazine products that are obtained (**6**) offer more functional diversity compared to **4**.

(1)

Based on our previous studies,^[9a,9c] Hashimoto's dirhodium carboxylate catalysts were considered to have the reactivity and selectivity suitable for high enantioselectivity in the [3+3]-cycloaddition reaction;^[12] however, although 100% conversion was obtained when the reaction was catalyzed by $\text{Rh}_2(\text{S-PTA})_4$ in DCM, only 5% enantiomeric excess (ee) was detected (Table 1, entry 1).^[13] Enantiomeric excess was increased to 45% by switching the solvent from DCM to methyl *tert*-butyl ether (TBME) or toluene with 71% and 100% conversion respectively (entries 2 and 3). Catalyst screening showed that increasing steric demand of the ligands on rhodium provided higher enantioselectivity (entries 3–8), which was opposite to previous results with reactions of enoldiazoacetates and nitrones^[9a] or hydrazones^[9c] (Scheme 1) in which the less sterically encumbered catalyst gave higher reactivity and selectivity. Further optimization with solvents (entries 9–12) gave **6a** in up to 93% ee in chloroform but there was only 26% conversion (entry 12). The outcome having the highest conversion/yield and %ee was obtained when the reaction was catalyzed by $\text{Rh}_2(\text{S-PTTL})_4$ ^[14] in fluorobenzene at 0 °C with 85% isolated yield and 90% ee (entry 9). Similar results were obtained with $\text{Rh}_2(\text{S-PTAD})_4$ ^[15] in fluorobenzene or toluene, which was also used for exploration (entries 13 and 14).

A variety of enoldiazoacetates **1** were examined under the optimized reaction conditions. As shown in Table 2, except for benzyl enoldiazoacetate **1e** (entry 5, 85% yield 77% ee), all of the TBS or TIPS protected enoldiazoacetates gave the corresponding bicyclic tetrahydropyridazines **6** in high yield with high to excellent enantioselectivity (entries 1–4

and 6–7, >75% yield, 90–95% *ee*). It is worth mentioning that enantioselectivity increased with increasing steric demand of the enoldiazoacetates **1** without affecting product yields. In our previously reported reactions of enoldiazoacetates 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 condition A offered higher yield.

The reaction scope was extended to substituted *N*-acyliminopyridinium ylides, and these results are summarized in Table 3. The steric and electronic properties of the substituents on the phenyl group had slight influences on 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 yield with 97% *ee* and 96% *ee* respectively (entries 6 and 7). In addition, with a 3-methyl group introduced to the pyridinium ring, high regioselectivity (>19:1) was found (Scheme 2, **6o** and **6o'**), [16] and 95% *ee* was obtained for the major isomer, while up to 32% *ee* was determined for the minor one. These results indicated that during the ring closing step the dirhodium catalyst is still associated with the substrate, and this association determines the outcome between the two possible positions. [17]

The (*S*)-configuration of the generated chiral 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 multi-functional groups, including ester, ether, acyl, and diene generated by dearomatization of *N*-acyliminopyridinium ylide. A one-pot reaction with *N*-phenylmaleimide to give the polycyclic product **7** in 77% yield with 2:1 *endo:exo* selectivity, and enantiomeric excesses for both of the diastereoisomers were the same as that of **6g** (Scheme 3).

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

Experimental Section

Condition A

To an oven-dried flask containing a magnetic stirring bar, *N*-acyliminopyridinium ylides **5** (0.20 mmol), 4 Å molecular Sieves (50 mg) and Rh₂(*S*-PTTL)₄ (2.0 mol%) in fluorobenzene (1.0 mL), was added enoldiazoacetates **1** (0.24 mmol) in fluorobenzene (0.5 mL) over 1 h period via a syringe pump at 0 °C, and the reaction mixture was stirred overnight. Following column chromatography on silica gel (eluent: hexanes:EtOAc = 100:0 to 90:10) pure tetrahydropyridazine derivatives **6** were obtained in high yield with high enantioselectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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 16. The two regioisomers were distinguished by 1D-nOe, see Supporting Information for details.
 17. When the reaction was catalyzed by Rh₂(OAc)₄, a 1:1 ratio of **60**:**60'** was obtained.
 18. See supporting information for details; CCDC 923840 contains the supplementary crystallographic data for **6i**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Figure 1.
(S)-Configuration of 6i is produced with catalysis by Rh₂(S-PTAD)₄.

Scheme 1.

Vinylogous dirhodium-enolcarbene formal [3+3]-cycloaddition reactions.

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

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

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

Table 1

Optimization of conditions for the enantioselective formal [3+3]-cycloaddition of enlodiazoacetate **1a** with **5a**.
[a]

Entry	Rh ₂ L ₄ (8)	Solvent	Conv., (%) ^[b]	ee (%) ^[c]
1	Rh ₂ (S-PTA) ₄ (8a)	DCM	100	5
2	Rh ₂ (S-PTA) ₄ (8a)	TBME	71	50
3	Rh ₂ (S-PTA) ₄ (8a)	toluene	100	50
4	Rh ₂ (S-PTL) ₄ (8b)	toluene	100	50
5	Rh ₂ (S-PTTL) ₄ (8c)	toluene	100	83
6	Rh ₂ (S-PTPA) ₄ (8d)	toluene	100	51
7	Rh ₂ (S-TCPTTL) ₄ (8f)	toluene	100	71
8	Rh ₂ (S-NTTL) ₄ (8g)	toluene	100	71
9	Rh ₂ (S-PTTL) ₄ (8c)	Fluorobenzene	91 (85) ^[d]	90
10	Rh ₂ (S-PTTL) ₄ (8c)	Chlorobenzene	95 (81) ^[d]	89
11	Rh ₂ (S-PTTL) ₄ (8c)	<i>o</i> -Xylene	100 (79) ^[d]	85
12	Rh ₂ (S-PTTL) ₄ (8c)	CHCl ₃	26	93
13	Rh ₂ (S-PTAD) ₄ (8e)	toluene	100 (88) ^[d]	89
14	Rh ₂ (S-PTAD) ₄ (8e)	Fluorobenzene	100 (86) ^[d]	89

[a] Reactions were carried out in a 0.2 mmol scale: **1a** (0.24 mmol), **5a** (0.20 mmol), 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 ¹H NMR spectra of reaction mixtures based on limiting reagent **5a**.

[c] Determined by HPLC analysis using chiral IA columns (Hexanes:*i*-PrOH = 94:6, 254 nm, 1.0 mL/min, t₁ = 8.7, t₂ = 12.4).

[d] Isolated yield of **6a** based on limiting reagent **5a**.

Table 2

Enantioselective formal [3+3]-cycloaddition of enlodiazoacetates **1** with **5a**.^[a]

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

^[a] Reactions were carried out in a 0.2 mmol scale: **1** (0.24 mmol), **5a** (0.20 mmol), 4 Å MS (50 mg), in 2.0 mL solvent with dirhodium catalyst (2.0 mol%), Condition A: catalyzed by Rh₂(S-PTTL)₄ in fluorobenzene; condition B: catalyzed by Rh₂(S-PTTL)₄ in toluene; condition C: catalyzed by Rh₂(S-PTAD)₄ in fluorobenzene; condition D: catalyzed by Rh₂(S-PTAD)₄ in toluene.

^[b] Isolated yield of **6** based on limiting reagent **5a**.

^[c] Determined by chiral HPLC analysis, see Supporting Information for details.

Table 3

Enantioselective formal [3+3]-cycloaddition of enoldiazoacetates **1g** with **5**.^[a]

Entry	5	Cond.	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	63	94		
		B	6m 72	96		
7	(5h)	D	6n 71	97		

^[a] Reactions were carried out in a 0.2 mmol scale: **1g** (0.24 mmol), **5** (0.20 mmol), 4 Å MS (50 mg), in 2.0 mL solvent with dirhodium catalyst (2.0 mol%). Condition A: catalyzed by Rh₂(S-PTTL)₄ in fluorobenzene; condition B: catalyzed by Rh₂(S-PTTL)₄ in toluene; condition C: catalyzed by Rh₂(S-PTAD)₄ in fluorobenzene; condition D: catalyzed by Rh₂(S-PTAD)₄ in toluene.

^[b] Isolated yield of **6** based on limiting reagent **5**.

^[c] Determined by chiral HPLC, see supporting information for details.

^[d] Reaction carried out on a 1.0 mmol scale.