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Dirhodium(II)-Catalyzed Formal [3+2+1]-Annulation of Azomethine Imines with Two Molecules of a Diazo Ketone

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Abstract

A highly diastereoselective formal [3+2+1]-cycloaddition reaction that produces multi-functionalized bicyclic pyrazolidinone derivatives is achieved in moderate to high yield by $\text{Rh}_2(4S\text{-MPPIM})_4$ -catalyzed reaction of azomethine imines with two molecules of a diazo ketone.

Cycloaddition reactions with azomethine imines,¹⁻⁴ stable and easily prepared iminium ylides that were first reported by Dorn in 1968,^{1a} have attracted considerable attention in dipolar [3+2]² and [3+3]³ cycloaddition reactions that are effective methodologies to access a diverse array of heterocycles.⁴ Specifically, Fu,⁵ Kobayashi,⁶ Toste,⁷ Hayashi,⁸ and we⁹ have separately studied azomethine imines in cycloaddition reactions that furnish five- and six-membered ring heterocycles. Although there are numerous intermolecular dipolar cycloaddition reactions reported between a dipole and a dipolarophile (Scheme 1), cyclization between three molecules is very rare.¹⁰ Herein we report a formal highly diastereoselective [3+2+1]-cycloaddition of azomethine imines with two molecules of a diazo ketone, catalyzed by $\text{Rh}_2(4S\text{-MPPIM})_4$, to give bicyclic pyrazolidinone derivatives in moderate to high yield.

Diazocarbonyl compounds have been extensively studied during the last few decades, and their applications in organic syntheses are well known.^{11,12} In our research, we have been investigating formal [3+3]-cycloaddition reactions of enoldiazoacetates **6** with 1,3-dipolar substrates.^{13,14} In these reactions, metal enol carbene intermediates, generated by dinitrogen extrusion with dirhodium(II) catalysts, showed electrophilic character at both the carbene and vinylogous positions (reaction sites 1 and 2 of **A** in Scheme 2) and can be regarded as versatile synthetic equivalents of pyruvates **7**. Based on this knowledge, we envisioned that dirhodium(II)-catalyzed decomposition of vinyl diazo ketone **4** would give metal carbene **B**, equivalent to diketone **8**, with three electrophilic carbon centers (reaction sites 1, 2 and 3 of **B**); and with this added functionality in metal carbene **B** additional synthetic opportunities would be possible.

With this in mind, the reaction of phenylazomethine imine **1a** with 4-methyl-1-diazo-3-buten-2-one **4** was investigated using dirhodium acetate as the catalyst (Table 1). The reaction was performed by adding the diazo ketone to a dichloromethane solution of **1a** and $\text{Rh}_2(\text{OAc})_4$ at room temperature (Table 1, entry 1). Although a complex mixture of products

was obtained, one compound was isolated in low yield whose surprising structure was determined to be **5** spectroscopically and by single-crystal X-ray diffraction analysis of its chloro derivative.¹⁵ This unexpected structure suggested that the azomethine imine **1a** reacted with two diazo ketone **4** to give the bicyclic pyrazolidinone derivative (*trans*-**5a**) as single isomer via a formal three-component [3+2+1]-cycloaddition. Efforts to increase the yield of **5a** by increasing the number of equivalents of diazo ketone **4** to 2.5 gave only a slightly higher conversion (entry 2). Scanning of dirhodium catalysts showed that the more Lewis acidic rhodium trifluoroacetate [Rh₂(tfa)₄] and rhodium perfluorobutyrate [Rh₂(pfb)₄] showed an expected higher reactivity in the decomposition of the diazoketone but exhibited no advantage over rhodium acetate in the formation of **5a** (entries 6 and 7). Rh₂(esp)₄ and Rh₂(cap)₄ caused decomposition of the diazo compound, but the process did not incorporate azomethine ylide in product formation (entries 3 and 5). Compared to the other tested catalysts, the chiral dirhodium(II) carboxamidate Rh₂(MPPIM)₄ (entry 9) gave the highest conversion (45%) and yield (39%). The yield was increased to 89% by using 4.0 equivalents of diazo ketone **4** relative to **1** (entries 10–12). With this catalyst (entry 11) and several other chiral dirhodium catalysts (entries 13–15) product analyses showed no enantiocontrol in the formation of **5a**. Copper and other Lewis acid catalysts did not form **5a**.¹⁶

With the optimized conditions in hand, reactions with a variety of azomethine imines were then examined. As shown in Table 2, the electronic properties of *para* substituents on the phenyl group of azomethine imines had an obvious influence on the yield; azomethine imines with both electron-rich and electron-deficient aryl substituents gave lower yields of **5** (entries 5 and 6) than those with methyl and halide substituents (entries 2–4). Substrates with *para*, *meta* or *ortho* substituents showed similar high reactivity (entries 2, 7 and 8). Notably, 1-naphthyl- and 1-furylazomethine imines were tolerated under these conditions and generated **5i** and **5j** in 73% and 64% isolated yield, respectively (entries 9 and 10). In addition, an alkyl substituted azomethine imine also reacted well and gave the corresponding pyrazolidinone in 61% yield (entry 11). Reactions with other diazocarbonyl compounds, including ethyl diazoacetate and diazoacetophenone, gave only carbene dimers from dinitrogen extrusion of the diazo compound with all of the azomethine imine remaining untouched.

The pathway to cycloaddition product **5** is perplexing, but there are a number of observations that lead to a proposed mechanism for the reaction: (1) adding diazo ketone **4** to the solution of **1** and rhodium catalyst at one time, or reversing the order of addition of reactants with diazo ketone added to the catalyst before azomethine imine **1**, resulted in complex mixtures of products and low or no production of **5** depending on the time that **1** was added following **4**; (2) dinitrogen extrusion from diazo ketones is slowed considerably in the presence of azomethine imine; and (3) effective enantiocontrol is absent with the use of chiral catalysts. These observations suggest that coordination of catalyst with azomethine imine precedes reaction with the diazo ketone and that a metal carbene generated from **4** is not involved in the formation of **5**. Accordingly, the role of the dirhodium catalyst is that of a Lewis acid to activate the azomethine imine for electrophilic addition to the diazo ketone (Scheme 3). Association of **1a** with dirhodium(II) compounds was verified by spectral shifts that occur in the visible region of the electromagnetic spectrum, as exemplified by the titration experiment with Rh₂(5*R*-MEPY)₄ (Figure 1) from which an association constant (K_{eq1}) of $57 \pm 8 \text{ M}^{-1}$ was determined.¹⁷ That Rh₂(cap)₄ does not undergo this formal [3 + 2 + 1]-cycloaddition is due to its inability to form a complex with **1**, but the same is not true with Rh₂(esp)₄ (K_{eq1} of $489 \pm 9 \text{ M}^{-1}$). Lower product yields with the more Lewis acidic dirhodium compounds, including Rh₂(esp)₄, may be due to their much greater reactivity towards the diazo ketone. Lewis acids including Cu(hfacac)₂, Sc(OTf)₃ and Zn(OTf)₂ did not provide sufficient activation of **1** to cause reaction with diazoketone **4**.¹⁶ There is in this transformation a delicate balance in the activation of **1** for electrophilic addition to the diazo

ketone versus either no addition or reaction of the catalyst with the diazo ketone independent of reaction with **1**.

In summary, we have discovered a diastereoselective formal [3+2+1]-cycloaddition that enables the efficient preparation of multi-functional bicyclic pyrazolidinone derivatives starting from azomethine imines and two molecules of a diazo ketone in moderate to high yield. This is a tactful annulation of three molecules catalyzed optimally by Rh₂(4*S*-MPPIM)₄. Additional studies with other diazoketones are underway to explore the scope of these reactions and to investigate alternative syntheses based on differential reactions with diazo ketones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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15. See supporting information for details; CCDC 904848 contains the supplementary crystallographic data for **5b**. These data can be obtained free of charge from the cambridge crystallographic data centre via www.ccdc.cam.ac.uk/data_request/cif
16. No product was obtained when the reaction was catalyzed by 5 mol% of CuPF_6 , $\text{Zn}(\text{OTf})_2$, $\text{Sc}(\text{OTf})_3$ or $\text{Cu}(\text{hfacac})_2$ under the optimized conditions.
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Figure 1.

Sequential aliquots of azomethine imine **1a** (2×10^{-3} mmol in 10 μ L DCM) added to $\text{Rh}_2(5R\text{-MEPY})_4$ (4×10^{-3} mmol in 2 mL DCM) gave a well-defined isosbestic point with an incremental shift of λ_{max} from 650 nm to 620 nm. K_{eq1} was calculated at three different wavelengths and the average K_{eq1} was determined to 57 ± 8 .

Scheme 1.
[3+3]-Cycloaddition of azomethine imines with various dipolarophile precursors.

Scheme 2.

Analogies between vinyl diazoacetates and vinyl diazoketones.

Scheme 3.

Proposed mechanism for the formal [3+2+1]-cycloaddition.

Table 1Optimization of conditions for the formal [3+2+1]-cycloaddition^a

entry	Cat.	4 (eq)	T (°C)	t (h)	conversion (%) ^b	yield (%) ^c
1	Rh ₂ (OAc) ₄	1.5	25	2	ND	23
2	Rh ₂ (OAc) ₄	2.5	25	2	35	ND
3	Rh ₂ (cap) ₄	2.5	40	12	<5 ^e	-
4	Rh ₂ (oct) ₄	2.5	25	12	15	ND
5	Rh ₂ (esp) ₄	2.5	25	2	<5 ^e	-
6	Rh ₂ (tfa) ₄	2.5	25	2	35	17
7	Rh ₂ (pfb) ₄	2.5	25	2	37	15
8	Rh ₂ (<i>S</i> -DOSP) ₄	2.5	25	2	34	23
9	Rh ₂ (4 <i>S</i> -MPPIM) ₄	2.5	40	12	45	39
10	Rh ₂ (4 <i>S</i> -MPPIM) ₄	5.0	40	12	>99	89
11 ^d	Rh ₂ (4 <i>S</i> -MPPIM) ₄	4.0	25	48	>99	89
12	Rh ₂ (4 <i>S</i> -MPPIM) ₄	3.0	25	48	87	81
13 ^d	Rh ₂ (5 <i>R</i> -MEPY) ₄	4.0	40	12	>99	73
14 ^d	Rh ₂ (<i>S</i> -DOSP) ₄	4.0	25	2	74	56
15 ^d	Rh ₂ (<i>S</i> -PTAP) ₄	4.0	25	2	82	63

^aReactions were carried out on a 0.3 mmol scale with **4** (indicated equivalent), **1a** (0.3 mmol), 4 Å MS (100 mg), in 2.0 mL DCM with 2.0 mol% of catalyst at the indicated temperature.

^bPercent conversion was determined from the proton NMR spectrum of the reaction mixture relative to limiting reagent **1a**.

^cIsolated yield of **5a** based on limiting reagent **1a**.

^dEnantioselectivity was determined by HPLC analysis using chiral AD-H columns (hexanes:*i*-PrOH = 95:5, 254 nm, 1.0 mL/min, t₁ = 7.8, t₂ = 11.9) and only <2% of *ee* was detected in all cases.

^eOnly decomposition of **4** was detected with unreacted **1a** recovered in high yield. ND = not detected.

Table 2

Azomethine imine substrate generality^a

entry	Ar (1)	5	dr ^b	yield (%) ^c
1	Ph (1a)	5a	> 95:5	90
2	4-ClC ₆ H ₄ (1b)	5b	> 95:5	85
3	4-BrC ₆ H ₄ (1c)	5c	> 95:5	89
4	4-MeC ₆ H ₄ (1d)	5d	> 95:5	79
5	4-MeOC ₆ H ₄ (1e)	5e	> 95:5	61
6	4-NO ₂ C ₆ H ₄ (1f)	5f	> 95:5	57
7	2-ClC ₆ H ₄ (1g)	5g	> 95:5	83
8	3-ClC ₆ H ₄ (1h)	5h	> 95:5	80
9	1-Naphthyl (1i)	5i	> 95:5	73
10	1-Furyl (1j)	5j	> 95:5	64
11	Cyclohexyl (1k)	5k	> 95:5	61

^aReactions were carried out on a 0.3 mmol scale: **4** (4.0 eq), **1** (0.3 mmol), 4 Å MS (100 mg), in 3.0 mL DCM with $\text{Rh}_2(4S\text{-MPPIM})_4$ (2.0 mol%) at room temperature.

^bDetermined by the proton NMR spectrum of the reaction mixture.

^cIsolated yield of **5** based on limiting reagent **1**.