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Bicyclic Pyrazolidinone Derivatives from Diastereoselective Catalytic [3 + 3]-Cycloaddition Reactions of Enoldiazoacetates with Azomethine Imines

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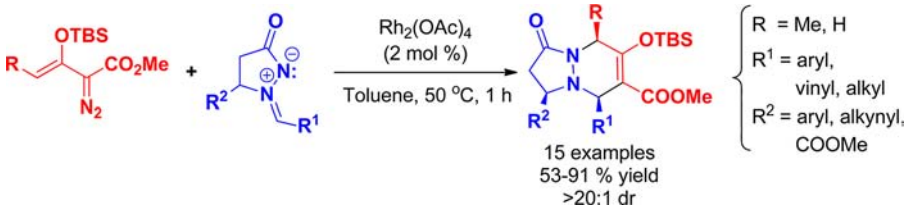
ABSTRACT



A highly regio- and diastereoselective synthesis of bicyclic pyrazolidinone derivatives by rhodium(II) acetate catalyzed [3 + 3]-annulation with enoldiazoacetates and azomethine imines has been achieved in high yield. A vinylogous reaction of the metal enol carbene with the azomethine imine initiates [3 + 3]-cycloaddition, whereas reaction at the carbene center effects N−N-cleavage of the azomethine imine.

Recent reports have demonstrated considerable interest in the development of effective methodologies for formal [3 + 3]-cycloaddition transformations[1] catalyzed by transition metal compounds[2,3] or organocatalysts.[4] Generation of metallovinylcarbene-like intermediates has been the key to successes in transition metal catalyzed reactions, as we have recently demonstrated through efficient and highly stereoselective formal [3 + 3]-cycloaddition reactions between hydrazones[3a] or nitrones[3b,c] and vinylcarbene intermediates derived from vinylogous attack of the electrophilic metal vinylcarbenes on nucleophilic reactants and are completed by intramolecular electrophilic addition that is coupled with catalyst dissociation (Scheme 1). They offer convenient methodologies for the synthesis of a diverse array of heterocyclic compounds in high yields and selectivities. In an effort to broaden the scope of [3 + 3]-cycloaddition reactions with conveniently

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(1) For reviews of [3 + 3]-cycloaddition reactions, see: (a) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703. (b) Buchanan, G. S.; Feltenberger, J. B.; Hsung, R. P. *Curr. Org. Synth.* **2010**, *7*, 363. (c) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, *1*, 23–44. (d) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1349.

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(4) (a) Hayashi, Y.; Toyoshima, M.; Gotoh, H.; Ishikawa, H. *Org. Lett.* **2009**, *11*, 45. (b) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (c) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao, J. -H. *Org. Lett.* **2006**, *8*, 2217. (d) Al-Harrasi, A.; Reißig, H.-U. *Angew. Chem., Int. Ed.* **2005**, *44*, 6227. (e) Helms, M.; Schade, W.; Pulz, R.; Watanabe, T.; Al-Harrasi, A.; Fisera, L.; Hlobilová, I.; Zahn, G.; H.-U. Reißig, H.-U. *Eur. J. Org. Chem.* **2005**, 1003. (f) Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. *J. Org. Chem.* **2005**, *70*, 4248.

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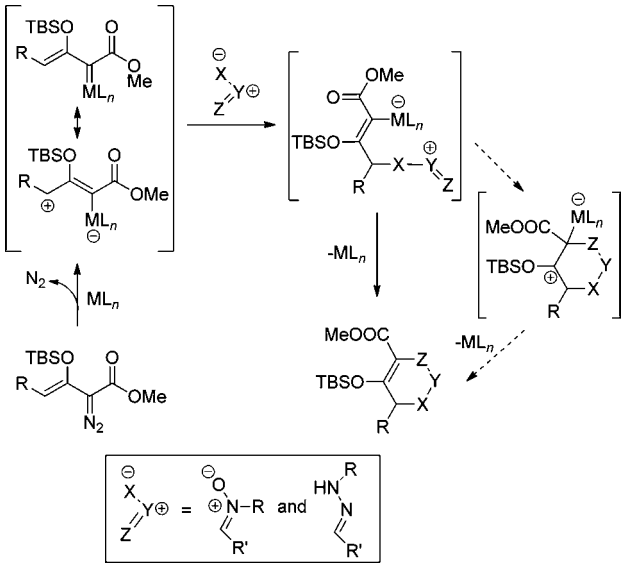
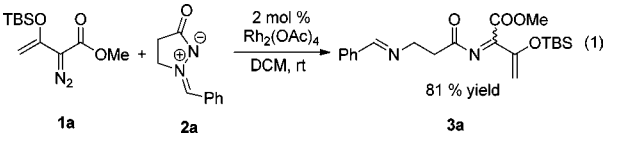
Scheme 1. [3 + 3]-Cycloaddition with Vinylcarbene Intermediates from Enoldiazoacetates and Dipolar Reactants

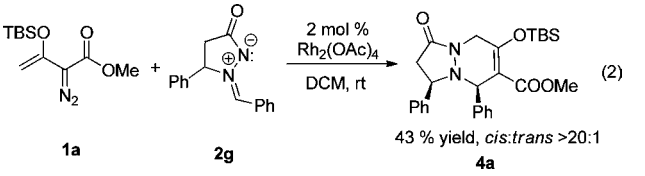


accessible enoldiazoacetates we have employed azomethine imine reactants,[5] whose ability to undergo cycloaddition has recently been reported with metal catalyst-derived vinylcarbenes derived from propargyl esters[2c] and (2-acetoxymethyl-2-propenyl)trimethylsilane.[2d]

Treatment of enoldiazoacetate **1a** with azomethine imine **2a** in the presence of a catalytic amount of rhodium acetate at room temperature in dichloromethane did not form a cycloaddition product as we had expected. Instead, this combination of reactants and catalyst resulted in the formation of diimine **3a** geometrical isomers in an apparent metal carbene-directed nitrogen−nitrogen cleavage reaction (eq 1). Ring fragmentation of a four-membered ring



azomethine imine has been noted in a gold-catalyzed reaction of a propargyl benzoate,[2c] but not in reactions of the five-membered ring azomethine imine analogs. In efforts to moderate this cleavage reaction, different azomethine imines (Figure 1) were employed with **1a**.[6] Replacement of the phenylimimium ion group in **2a** by the *trans*-styryliminium group did not change the reaction outcome, and different alkyl substituents at the 4- and 5-positions of the azomethine imines (**2b**−**2f**) also showed dominant or complete N−N cleavage. However, phenyl substitution at the 5-position facilitated formal [3 + 3]-cycloaddition which occurred in 43% yield with complete diastereocontrol (eq 2) without evidence of N−N cleavage.



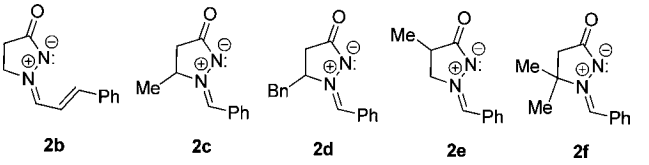


Figure 1. Azomethine imines that underwent predominant ring fragmentation in rhodium acetate catalyzed reactions with enoldiazoacetate **1a**.

To ascertain the generality of this cycloaddition process, representative copper, silver, and gold catalysts were also used, and optimization of reaction conditions was performed (Table 1). Silver triflate gave a complex mixture whose contents were not pursued. Treatment with copper(II) triflate or $AuCl_3$ only produced the [3 + 2]-cycloaddition product **5a** in high yield,[7] although with low diastereocontrol in the case of $AuCl_3$ catalysis. Rhodium(II) acetate formed the [3 + 3]-cycloaddition product **4a** as the sole diastereoisomer without evidence for **5a**, and optimization was performed with this catalyst. Very low azomethine imine and catalyst solubilities prevented reaction in hexane, and THF coordination with rhodium acetate limited effective catalysis. However, use of 1,2-dichloroethane improved the yield to 69% from 43% obtained in dichloromethane, and a further increase in yield occurred for the reaction performed in toluene. Increasing the reaction temperature to 50 °C favored [3 + 3]-cycloaddion with an even higher 85% yield without a decrease in diastereocontrol, but a further increase in the reaction temperature gave a slightly lower product yield.

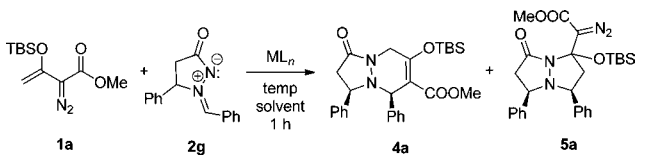
The tolerance of azomethine substituents R^1 to this [3 + 3] cycloaddition reaction was evaluated under optimized reaction conditions, and the results obtained are summarized in Table 2. In all cases, the reaction proceeded smoothly to give cycloaddition products **4a**−**j** in good to high yields (52%−91%) with exclusive *cis* diastereoselectivities

(5) For recent selected examples of the cycloadditions of azomethine imines, see: (a) Imaizumi, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 20049. (b) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J. C.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Guo, H. C.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337. (c) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076. (d) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 6330. (e) Suarez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 1124. (f) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778. For a report that describes the stabilities and importance of azomethine imines, see: (g) Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A. B.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16111 and references therein.

(6) Azomethine imines **2a**−**2f** formed diimines **3** as the sole or major products; however, diimines **3** are unstable on silica gel, and only **3a** and **3f** were successfully isolated and fully characterized.

(7) Xu, X.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 1244.

Table 1. Optimization of the [3 + 3]-Annulation of OTBS-Substituted Enoldiazoacetate **1a** and Azomethine Imine **2g**[a]



entry	ML_n	solvent	temp (°C)	yield, %[b] 4a	yield, %[b] 5a	dr[c] (*cis*/*trans*)
1	AgOTf	CH_2Cl_2	23	complex mixture		–
2	$Cu(OTf)_2$	CH_2Cl_2	23	–	74	>20:1
3	$AuCl_3$	CH_2Cl_2	23	–	91	3:2
4	$Rh_2(OAc)_4$	CH_2Cl_2	23	43	–	>20:1
5	$Rh_2(OAc)_4$	$CHCl_3$	23	64	–	>20:1
6	$Rh_2(OAc)_4$	$ClCH_2CH_2Cl$	23	69	–	>20:1
7	$Rh_2(OAc)_4$	toluene	23	74	–	>20:1
8	$Rh_2(OAc)_4$	toluene	50	85	–	>20:1
9	$Rh_2(OAc)_4$	toluene	80	81	–	>20:1

[a] Reactions were performed by the dropwise addition over 1 h of enol diazoacetate **1a** (0.75 mmol) in 1 mL of solvent to the mixture of azomethine imine **2g** (125 mg, 0.50 mmol) and catalyst (2.0 mol %) in 4 mL of solvent. [b] Isolated yield after column chromatography. [c] Diastereoselectivities were determined by ^{1}H NMR spectral analyses of the unpurified reaction mixture.

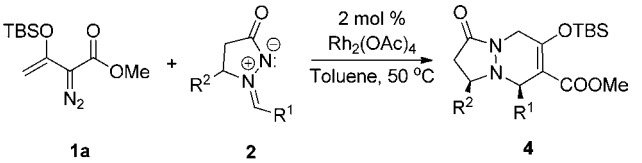
(> 20:1 dr). Use of electron-donating substituents in R^1 resulted in higher yields of the corresponding cycloaddition products than when R^1 had electronic-withdrawing substituents. In addition, R^1 as furyl (entry 8) or styryl (entry 9) did not diminish reactivity or selectivity (> 20:1 dr). Notably, R^1 as cyclohexyl (entry 10) also provided the cycloaddition product in moderate yield with a high diastereomeric ratio.

Changing the substituent R^2 of the azomethine imime from phenyl to substituted phenyl (entries 11 and 12, Table 2) had no adverse effect on either reactivity or selectivity. Remarkably, the azomethine imine with an alkynyl substituent or even an ester group provided [3 + 3]-annulation products **4m** and **4n** in good yield with only the *cis* stereochemistry as confirmed by single-crystal X-ray analysis of **4b** (Table 2, entry 2; Figure 2).[8] In contrast, ring fragmentation is the outcome with R^2 = H, Me, and Bn, and the cause for this disparity appears to be linked to subtle steric and/or stereoelectronic factors.

Enoldiazoacetate **1b**, in which a methyl group has replaced hydrogen in the 4-position, also favored [3 + 3] cycloaddition; the desired product **6** was obtained in high 81% yield, and only the all-*cis* isomer was observed (eq 3) as established by NOE experiments. However, phenyl substituted enoldiazoacetate **1c** did not undergo

(8) CCDC 898785 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

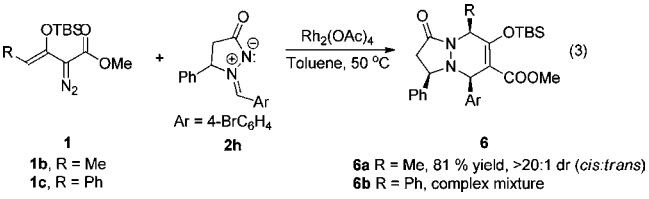
Table 2. Rhodium(II) Acetate Catalyzed [3 + 3]-Annulation of Enoldiazoacetate **1a** and Azomethine Imines **2**[a]



entry	R^1	R^2	4	yield 4, %[b]	dr 4[c] (*cis*:*trans*)
1	Ph	Ph	**a**	85%	> 20:1
2	4-BrC_6H_4	Ph	**b**	81%	> 20:1
3	4-$MeOC_6H_4$	Ph	**c**	91%	> 20:1
4	4-$NO_2C_6H_4$	Ph	**d**	61%	> 20:1
5	4-ClC_6H_4	Ph	**e**	83%	> 20:1
6	3-BrC_6H_4	Ph	**f**	78%	> 20:1
7	4-MeC_6H_4	Ph	**g**	80%	> 20:1
8	*trans*-styryl	Ph	**h**	89%	> 20:1
9	2-furyl	Ph	**i**	88%	> 20:1
10	cyclohexyl	Ph	**j**	53%	> 20:1
11	Ph	4-BrC_6H_4	**k**	82%	> 20:1
12	Ph	4-$MeOC_6H_4$	**l**	87%	> 20:1
13	Ph	TMS—≡—	**m**	86%	> 20:1
14	Ph	CO_2Me	**n**	71%	> 20:1

[a] Reactions were performed by the dropwise addition over 1 h of enoldiazoacetate **1a** (0.75 mmol) in 1 mL of toluene to the mixture of azomethine imine **2** (0.50 mmol), and $Rh_2(OAc)_4$ (2.0 mol %) in 4 mL of toluene at 50 °C. [b] Isolated yield after column chromatography. [c] Diastereoselectivities were determined by ^{1}H NMR spectral analyses of the unpurified reaction mixture and were greater than 20:1 in all cases.

reaction with azomethine ylides, presumably because of steric encumbrance.



The pathway for this formal [3 + 3] annulation reaction is triggered by Rh(II) catalyzed dinitrogen extrusion from enoldiazoacetate **1** that forms an electrophilic rhodium vinylcarbene which undergoes either carbenic carbon or vinylogous attack on the nucleophilic nitrogen of the azomethine imine to form adduct **7** or **8** (Scheme 2). The formation of **6a** is consistent with steric control in the formation of **8**. Subsequent ring formation from **8** followed by extrusion of the catalyst gives the dinitrogen-fused heterocyclic ring.[9] The high diastereoselectivity in this reaction can be rationalized by minimization of unfavorable steric interactions between the dirhodium

(9) Dinitrogen-fused heterocyclic ring displays broad biological activities; see: (a) Konaklieva, M. I.; Plotkin, B. *J. Curr. Med. Chem. Anti-Infect. Agents* **2003**, *2*, 287. (b) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, 2003. (c) Varvounis, G.; Fiamegos, Y.; Pilidis, G. *Adv. Heterocycl. Chem.* **2001**, *80*, 73.

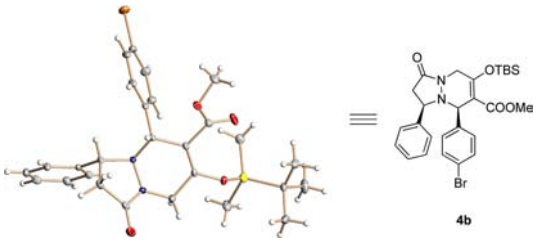
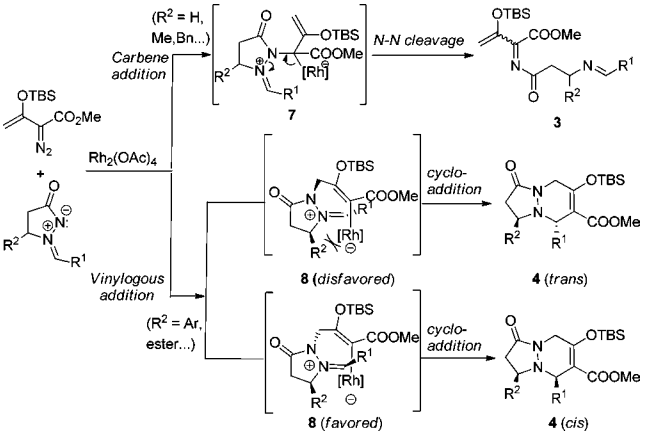


Figure 2. X-ray structure of bicyclic pyrazolidinone **4b**.

position and R^2 in the transition state that accompanys ring closing. Alternatively, the metal-associated ylide **7** preferentially undergoes N−N cleavage to form diimine **3**. The discrimination between the pathways leading to intermediates **7** and **8** has its origin in the steric and/or electronic nature of R^2, but the precise cause is unknown.

In summary, we have developed a highly efficient way to prepare *N,N*-bicyclic pyrazolidinone derivatives by rhodium(II) acetate catalyzed [3 + 3]-annulation with enoldiazoacetate and azomethine imines that occur in high yield and, to the extent that we can measure, complete regio- and diastereocontrol. The azomethine imines with aryl and polar substituents at the 5-position selectively attack the vinylogous position of the Rh(II)-vinyl carbenes rather than at the carbene center. Research is currently underway to demonstrate the use of this methodology for other [3 + 3]-cycloaddition reactions.

Scheme 2. Proposed Pathway for Rh(II) Catalyzed [3 + 3]-Annulation of Electrophilic Vinylcarbene and Azomethine Imines



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Supporting Information Available. General experimental procedures, the X-ray structure of **4b**, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.