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Highly Regio- and Enantioselective Formal [3 + 2]-Annulation of Indoles with Electrophilic Enol Carbene Intermediates

Changcheng Jing,[†] Qing-Qing Cheng,[‡] Yongming Deng,[‡] Hadi Arman,[‡] and Michael P. Doyle*[,‡]

[†]Shanghai Engineering Research Centre of Molecular Therapeutics and New Drug Development, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, P.R. China

[‡]Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States

Supporting Information

ABSTRACT: Chiral cyclopentane-fused indolines are synthesized with high regio- and enantiocontrol by formal [3 + 2]-annulation reactions of indoles and electrophilic enol carbenes. High enantioselectivity and exclusive regiocontrol occurred with enoldiazoacetamides using a less sterically encumbered prolinate-ligated dirhodium(II) catalyst in reactions with *N*-substituted indoles without substituents at the 2- or 3-positions via a selective vinylogous addition process. In this transformation, donor−acceptor cyclopropenes generated from enoldiazoacetamides serve as the carbene precursors to form metal carbene intermediates.

C2,C3-Fused indole skeletons are key structural motifs of a large number of alkaloid natural products and bioactive compounds,[1] and considerable effort has been focused on the development of chemo-, regio-, and enantioselective methodologies to form C2,C3-fused indoles and indolines.[2−4] Of the synthetic methods that have been developed, dearomatizing [3 + 2]-annulation of indoles has proven to be an efficient and effective approach to cyclopentane−fused indole-derived alkaloids[3,4] which are common structures in bioactive compounds (Figure 1).[1,5] However, in spite of longstanding

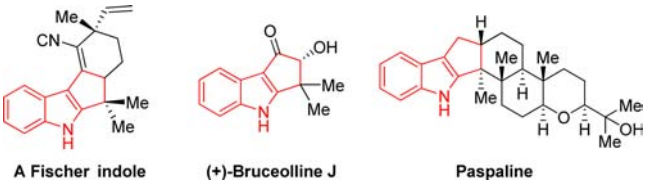

Figure 1. Cyclopent[*b*]indole alkaloids.

efforts, only limited reports are available on catalytic asymmetric methods for their synthesis.[4] Barluenga reported an enantioselective [3 + 2]-cycloaddition reaction of indoles with tungsten Fischer alkynylcarbenes using (*S*)-menthol as a chiral auxiliary,[4a] while Davies realized an enantioselective dirhodium-catalyzed version with styryldiazoacetates,[4b] and Tang developed a copper-catalyzed enantioselective intramolecular cyclopentane-annulation of indoles with donor−acceptor cyclopropanes.[4c,d] However, in all of these cases, indoles with electron-donating alkyl groups at the 2- or 3-position were required in order to achieve regio- and stereocontrol.[4b] Regioselectivity was explained by the steric preferences of s-*trans*- and s-*cis*-metallo-styrylcarbenes in reactions with 1,2- and 1,3-disubstituted indoles or by different styryl group orientations of zwitterionic intermediates in the [3 + 2]-cycloaddition reaction.[4b] Dearomatizing [3 + 2]-annulation of indoles without substitution at the 2- or 3-positions that occurs with good chemo-, regio-, and enantiocontrol has not been achieved.

Electrophilic enol carbene intermediates generated from enoldiazo compounds are 1,3-dipole equivalents that possess electrophilic character at the vinylogous position and nucleophilic character at the metal carbene carbon. These intermediates readily undergo [3 + 3]-annulation reactions with 1,3-dipoles[6] or [3 + 2]-annulation reactions with unsaturated compounds having nucleophilic character.[7] Could vinylogous reactivity from these vinylcarbene intermediates also provide high regioselectivity and enantioselectivity for [3 + 2]-annulation of indoles without substituents at either the 2- or 3-positions?

Treatment of 1.2 equiv of enol diazoacetate **1** with 1.0 equiv of 1-methylindole **2a** in the presence of 2 mol % of dirhodium tetraacetate and 4 Å MS in $CHCl_3$ at room temperature gave, as expected from Davies' prior report,[4b] two regioisomeric [3 + 2]-annulation products in a 44:56 ratio (68% yield). An extensive screening of chiral dirhodium catalysts was conducted in efforts to improve regioselectivity as well as to achieve enantiocontrol (Scheme 1).[8] Chiral phthalimidate-ligated dirhodium carboxylate catalysts favored addition to indole from the carbene carbon to give **4** as a major product in variable ratios, but use of the more Lewis acidic Rh_2(*S*-TFPTTL)$_4$ gave the highest regioselectivity and enantioselectivity for the formation of this product. Switching to prolinate-derived catalysts resulted in reversed regioselectivities with vinylogous addition forming **3** as the major product. However, both chiral

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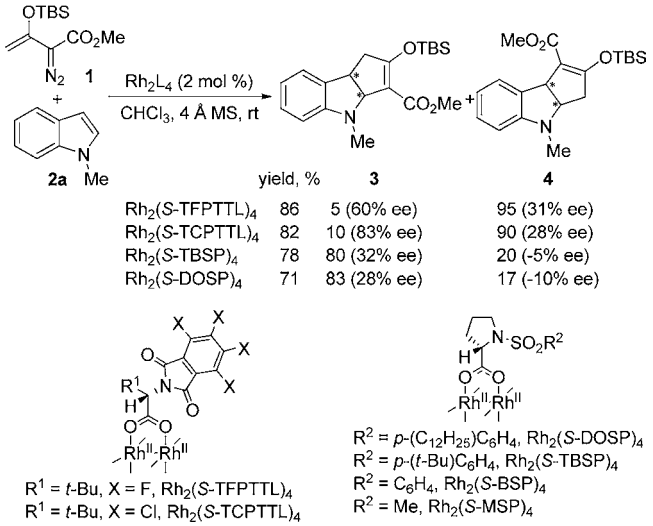
Scheme 1. Catalytic [3 + 2]-Annulation of Indole 2a with Enol Diazoacetate 1

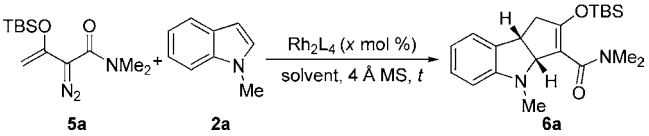


phthalimide rhodium carboxylate catalysts and chiral prolinate-derived catalysts gave the [3 + 2]-annulation products with poor enantioselectivities.

Given our recent successes in the uses of enoldiazoacetamides as highly selective reagents for vinylogous cycloaddition reactions,[6e,9] we considered their use for reactions with 1-methylindole. Initial reactions were conducted in $CHCl_3$ by slowly adding a solution of enoldiazoacetamide **5a** to a mixture of indole **2a**, 1.0 mol % $Rh_2(OAc)_4$, and 4 Å MS at room temperature. After 4 h, the [3 + 2]-cycloaddition product **6a** was isolated in 18% yield as a single regioisomer. The screening of different catalysts was conducted to maximize the efficiency and selectivities of this [3 + 2]-annulation transformation.[8] Use of $Cu(MeCN)_4PF_6$ and $Cu(OTf)_2$ with (*S*,*S*)-*t*-Bu-Box ligand gave the desired product in low yield, but without any enantioselectivity, and with $AgSbF_6$ in place of copper catalysts no activity was observed. The use of phthalimide-amino acid ligated dirhodium catalysts did not give the [3 + 2]-annulation product after 4 h at room temperature. However, the more Lewis acidic Rh_2(*S*-TFPTTL)$_4$ catalyzed the formation of only one regioisomer (**6a**) in 33% yield, but this catalyst did not provide enantiocontrol (Table 1, entry 1). Switching to known prolinate-derived catalysts resulted in significant increases in both the yields and enantioselectivities for the [3 + 2]-annulation product **6a** (Table 1, entries 2−4), but enantioselectivities remained low.

With recognition from a previously reported [3 + 3]-cycloaddition reaction of enoldiazoacetates[10] that a less sterically encumbered catalyst could give higher enantioselectivities, we prepared the methanesulfonyl analogue of the arylsulfonylprolinate ligated dirhodium(II) carboxylates, Rh_2(*S*-MSP)$_4$, and applied this catalyst to the reaction between **2a** and **5a** which gave the highest level of enantiocontrol (Table 1, entry 5). Using Rh_2(*S*-MSP)$_4$, other reaction parameters (solvent, reaction temperature, reaction time, and the loading of the catalyst) were examined, and representative results are reported in the table.[8] Low reaction temperatures and use of toluene gave higher enantioselectivities, but reactions were sluggish (Table 1, entries 6 and 7). Increasing the catalyst loading of Rh_2(*S*-MSP)$_4$ to 2 mol % in chloroform accelerated the reaction rate (Table 1, entry 8). The [3 + 2]-annulation

Table 1. Optimization of the [3 + 2]-Annulation Reaction of *N*-Methylindole 2a with *N*,*N*-Dimethyl Enoldiazoacetamide 5a[a]



entry	Rh_2L_4 (*x*)	solvent	temp (°C)	yield[b] (%)	ee[c] (%)
1	Rh_2(*S*-TFPTTL)$_4$ (1)	$CHCl_3$	rt	33	0
2	Rh_2(*S*-DOSP)$_4$ (1)	$CHCl_3$	rt	18	43
3	Rh_2(*S*-BSP)$_4$ (1)	$CHCl_3$	rt	49	48
4	Rh_2(*S*-TBSP)$_4$ (1)	$CHCl_3$	rt	32	46
5	Rh_2(*S*-MSP)$_4$ (1)	$CHCl_3$	rt	55	80
6	Rh_2(*S*-MSP)$_4$ (1)	toluene	rt	13	90
7	Rh_2(*S*-MSP)$_4$ (1)	$CHCl_3$	0	11	88
8	Rh_2(*S*-MSP)$_4$ (2)	$CHCl_3$	0	61	88
9	Rh_2(*S*-MSP)$_4$ (2)	$CHCl_3$/ toluene	rt	45	91
10[d]	Rh_2(*S*-MSP)$_4$ (2)	$CHCl_3$/ toluene	0	82	94

[a]Unless otherwise noted, all reactions were conducted on a 0.10 mmol scale of **2a** with **5a**/**2a** = 1.2:1.0. Diazoamide **5a** in 0.5 mL of solvent was added to the mixture of catalyst, **2a**, and 4 Å MS (100 mg) in 0.5 mL of solvent by syringe pump over 30 min, and then the reaction mixture was stirred for 4 h. [b]Isolated yields obtained after column chromatography. [c]Determined by HPLC using a chiral column. [d]The reaction mixture was stirred for 24 h.

product **6a** was obtained in 45% yield and 91% ee when a mixed solvent of 1:1 $CHCl_3$ and toluene was used (Table 1, entry 9). Prolonging the reaction time to 24 h and lowering the reaction temperature to 0 °C further improved the yield and enantioselectivity (82% yield, 94% ee; Table 1, entry 10), and these conditions were optimal. Use of Rh_2(*S*-MSP)$_4$ with **1** gave **3** (31% ee) and **4** (−10% ee) in a 79:31 ratio (68% yield).[8]

With the optimal conditions in hand, we probed the reaction scope for this formal [3 + 2]-annulation transformation. The size of the amide group had a significant impact on the level of enantioselectivity. Enoldiazoacetamide **5b** that bears a piperidine ring gave the [3 + 2]-annulation product with higher enantioselectivity than did *N*,*N*-dimethyl enoldiazoacetamide **5a** (Scheme 2, **6b** vs **6a**). In general, excellent regio- and enantioselectivities were obtained regardless of the substituents on nitrogen atom or on the benzene ring of the examined indoles. *N*-Benzyl indole gave the [3 + 2]-annulation product in lower yield than did *N*-methylindole although their enantioselectivities were similar (Scheme 2, **6c** vs **6b**). Indoles bearing different electron-withdrawing benzene substituents were generally less reactive (Scheme 2, **6g**−**6j** vs **6d**−**6f**), probably due to their reduced nucleophilicity. 6-Chloro- and 7-chloro-substituted indoles gave slightly higher enantioselectivities than did the 5-chloro-substituted indole; however, use of 7-chloro-substituted indole resulted in a reduced yield (Scheme 2, **6h**−**6j**). Surprisingly, indoles possessing a methyl group at either the 2- or 3-positions did not give the [3 + 2]-annulation products with enoldiazoacetamides **5** as they did in reactions with (*E*)-arylvinyldiazoacetates reported by Davies and coworkers;[4b] instead **5** was converted to its derivative donor−acceptor cyclopropene without reacting with **2**.

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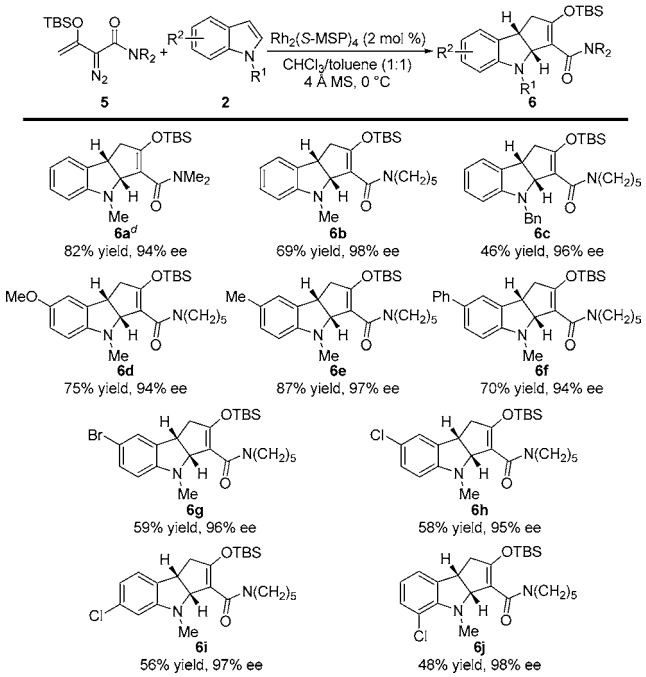
Scheme 2. Reaction Scope[a−c]



[a]Unless otherwise noted, all reactions were conducted on a 0.20 mmol scale of **2** with **5**/**2** = 1.2:1.0. **5** in 1.0 mL of solvent ($CHCl_3$/toluene = 1:1) was added to the mixture of Rh_2(*S*-MSP)$_4$ (2 mol %), **2**, and 4 Å MS (200 mg) in 1.0 mL of solvent ($CHCl_3$/toluene = 1:1) by syringe pump over 30 min at 0 °C, and then the reaction mixture was stirred for 48 h at the same temperature. [b]% yield refers to isolated yields of the product after column chromatography, and the only other indole-derived material observed in the reaction mixture was the unreacted indole **2**. [c]% ee was determined by HPLC using a chiral column. [d]The reaction mixture was stirred for 24 h.

The relative configuration of the product *rac*-**6g** was determined by X-ray crystallographic analysis (Figure 2).[11]

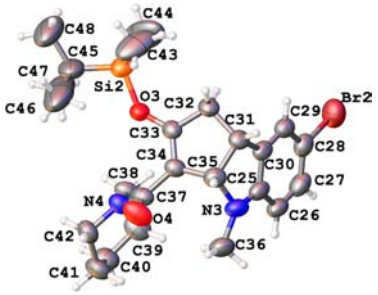
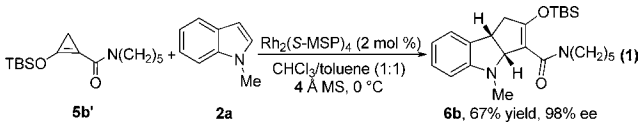


Figure 2. X-ray structure of [3 + 2]-annulation product *rac*-**6g**.

The absolute configuration of the [3 + 2]-annulation product was determined as (3a*R*,8b*S*) by comparison of the observed optical rotation with the sign of the specific rotation of similar structures.[4b,12]

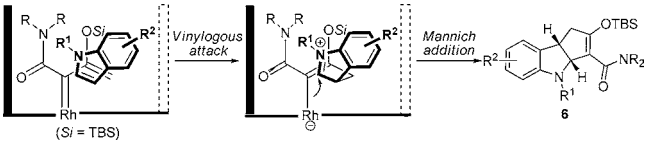
In our previous work, donor−acceptor cyclopropenes generated from enoldiazo compounds have served as carbene precursors to take part in cyclopropanation[13] and C−H insertion reactions.[9a] Close spectroscopic inspection of the reaction of 1-methylindole **2a** with enoldiazoacetamide **5b** indicated that formation of donor−acceptor cyclopropene was much faster than the generation of [3 + 2]-annulation products.[12] To further determine if the donor−acceptor cyclopropene is the carbene precursor in this transformation, the reaction of 1-methylindole **2a** with cyclopropene **5b′**, thermally preformed from enoldiazoacetamide **5b**,[13] was performed under the same conditions as the reactions reported in Scheme 2 (eq 1). The [3 + 2]-annulation product **6b** was



obtained with the same selectivity in similar yield (67% yield, 98% ee) as with diazo compound **5b**. Additionally, the optimal catalyst in the present system [Rh_2(*S*-MSP)$_4$] was also evaluated in other carbene-transfer reactions.[12] In comparison with the established dirhodium(II) prolinate catalyst Rh_2(*S*-DOSP)$_4$, the sterically less demanding Rh_2(*S*-MSP)$_4$ provided lower stereocontrol in cyclopropanation of styrene [65% ee, 13:1 dr with Rh_2(*S*-MSP)$_4$; 91% ee, > 20:1 dr with Rh_2(*S*-DOSP)$_4$[14]] and C−H insertion into cyclohexane with *α*-phenyl-*α*-diazoacetate [15% ee with Rh_2(*S*-MSP)$_4$; 88% ee with Rh_2(*S*-DOSP)$_4$[15]], however, giving higher enantioselectivity in [3 + 3]-cycloaddition of *N*,*α*-diphenyl nitrone with enoldiazoacetate [20% ee with Rh_2(*S*-MSP)$_4$; 0% ee with Rh_2(*S*-DOSP)$_4$[10]].

An explanation for the observed regio- and enantioselectivity that is achieved with the metal carbene formed by catalytic reactions of enoldiazoacetamides with *N*-substituted indoles is given in Scheme 3. Rhodium-catalyzed metal carbene formation

Scheme 3. Proposed Mechanism for [3 + 2]-Cycloaddition



from the enoldiazo compound or its derivative donor−acceptor cyclopropene affords a preferred *s-cis*-vinylcarbene to minimize the steric interaction between the internal OTBS group and the "wall" of rhodium catalyst. Upon vinylogous attack by the indole, a configurationally stable vinylrhodium intermediate linked to the electrophilic indoleniminium ion is formed. Indoleniminium ion addition to the vinyl carbon bound to rhodium is facilitated by stabilization that is provided by the OTBS group. Release of the rhodium catalyst gives the [3 + 2]-annulation product. Note that this explanation is consistent with the lower yield of cycloaddition product formed with *N*-benzylindole than with *N*-methylindole and with the enhancement of enantioselectivity from the piperidine amide **5b** relative to the dimethylamine **5a**. Regioselectivity is imposed on the cycloaddition process by the amide functionality of the metallo-enolcarbene.

In conclusion, we have demonstrated the high regio- and enantioselectivities for Rh_2(*S*-MSP)$_4$-catalyzed dearomatizing [3 + 2]-annulation of indoles and enoldiazoacetamides and metal carbene formation that produces the C2,C3-fused indoline products occurs through the intermediate donor−acceptor cyclopropene. The acyl group of the enol carbene intermediate is a determining factor for selective vinylogous reactivity. Reactions with indole substrates without methyl substituents at either the 2- or 3-positions and less sterically

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encumbered catalyst ligands allow for the efficient synthesis of enantioenriched cyclopentane-fused indoline building blocks via a selective vinylogous addition process. Extending this transformation to other nucleophiles, as well as exploring the importance of donor−acceptor cyclopropenes and the effect of different acyl groups on vinylcarbene intermediate, comprises our future interests.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02192.

General experimental procedures, results from detailed surveys of yields and selectivities for reaction optimizations, and spectroscopic data for all new compounds (PDF)

X-ray data for *rac*-**6g** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: michael.doyle@utsa.edu.

Notes

The authors declare no competing financial interest.

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(8) See the Supporting Information for a detailed survey of yields and enantioselectivities.

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(11) CCDC 1420593 (*rac*-**6g**) 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.

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