Annulation

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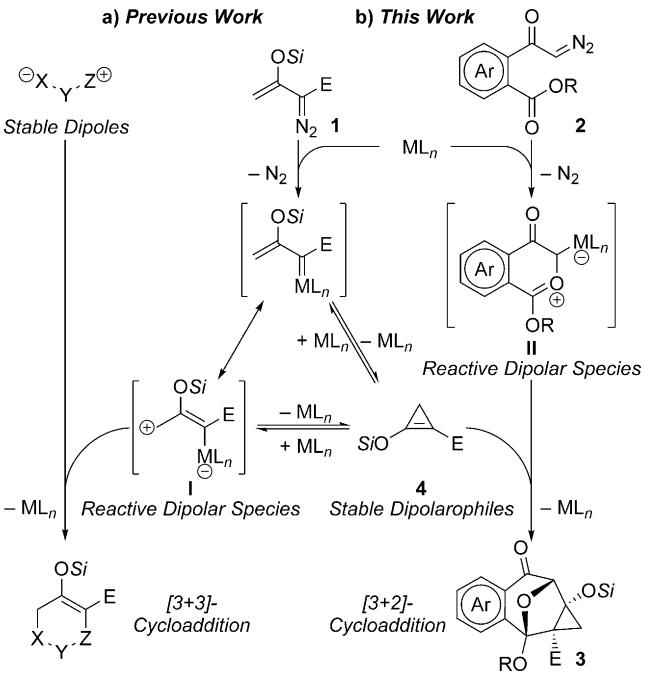
Dirhodium(II)-Catalyzed Annulation of Enoldiazoacetamides with α-Diazoketones: An Efficient and Highly Selective Approach to Fused and Bridged Ring Systems

*Qing-Qing Cheng, Julietta Yedoyan, Hadi Arman, and Michael P. Doyle**

Abstract: *A dirhodium(II)-catalyzed annulation reaction between two structurally different diazocarbonyl compounds furnishes the donor–acceptor cyclopropane-fused benzoxa-[3.2.1]octane scaffold with excellent chemo-, regio-, and diastereoselectivity under exceptionally mild conditions. The composite transformation occurs by [3+2]-cycloaddition between donor–acceptor cyclopropenes generated from enoldiazoacetamides and carbonyl ylides formed from intramolecular carbene–carbonyl cyclization in one pot with one catalyst. The annulation products can be readily transformed into benzoxa[3.3.1]nonane and hexahydronaphthofuran derivatives with exact stereocontrol. This method allows the efficient construction of three fused and bridged ring systems, all of which are important skeletons of numerous biologically active natural products.*

Transition-metal-catalyzed annulation reactions are among the most powerful tools for organic synthesis, providing efficient and highly selective approaches to various ring systems. In previous studies, diazo compounds have proven to be easily accessible and versatile reagents for these transformations.[1] Enoldiazo compounds **1** were most commonly employed as precursors of metallo-enolcarbenes **I** that served as reactive dipolar species in formal [3+3]-cycloadditions with stable dipoles (Scheme 1 a),[1d,2] as well as in other [3 + *n*]-cycloaddition processes (*n* = 2, 4, 5).[3] The success of these reactions prompted us to ask if similar transformations could be realized with other reactive dipolar species in the presence of enoldiazo compounds. Since α-diazoketones **2** undergo dinitrogen extrusion to generate carbonyl ylides **II** (another class of energetic dipolar intermediates in cycloaddition reactions),[1b,c,4] could the combination of diazo compounds **1** and **2** furnish annulation product(s) with high selectivity? Notably, a transition-metal-catalyzed annulation reaction between two structurally different diazo compounds remains unknown, mainly because it is more challenging to achieve compatible reactivity and controllable selectivity between two distinct in situ generated intermediates. Inspired by our previous observations of donor–acceptor cyclopropenes **4** as important intermediates in metal-catalyzed enolcarbene transformations,[2d,5] we envisioned that, upon identification of a suitable catalyst and compatible reagents, annulation reactions between diazo compounds **1** and **2** could be achieved through a cascade cyclopropene and carbonyl ylide formation/[3+2]-cycloaddition process (Scheme 1 b). Herein, we report the outcome of our investigation. The developed reaction furnishes unique benzoxa[3.2.1]octane scaffolds bearing highly strained donor–acceptor cyclopropane moieties, which provides further access to benzoxa-[3.3.1]nonane and hexahydronaphthofuran derivatives via selective ring opening and rearrangement (Scheme 2 a). Moreover, all the above three ring systems are important skeletons of numerous biologically active natural products (Scheme 2 b).[6]



Scheme 1. Transition-metal-catalyzed annulation reactions of enoldiazo compounds. M = transition metal, L = ligand, *Si* = silyl protecting group, E = electron-withdrawing group, Ar = aryl group.

In the initial study, we conducted the reaction of *tert*-butyldimethylsilyl (TBS)-protected enoldiazoacetamide **1a** with *o*-methoxycarbonyl-α-diazoacetophenone **2a** in chloroform ($CHCl_3$) at room temperature, and a selection of commercially available dirhodium(II) complexes were evaluated as catalysts (Table 1, entries 1–5). In the presence of 2 mol% of rhodium(II) acetate [$Rh_2(OAc)_4$], annulation product **3aa** was formed in a promising 56% yield with a diastereomeric ratio of 5:1, while the dimerization of carbonyl ylide generated from **2a** (compound **5a**) was a major

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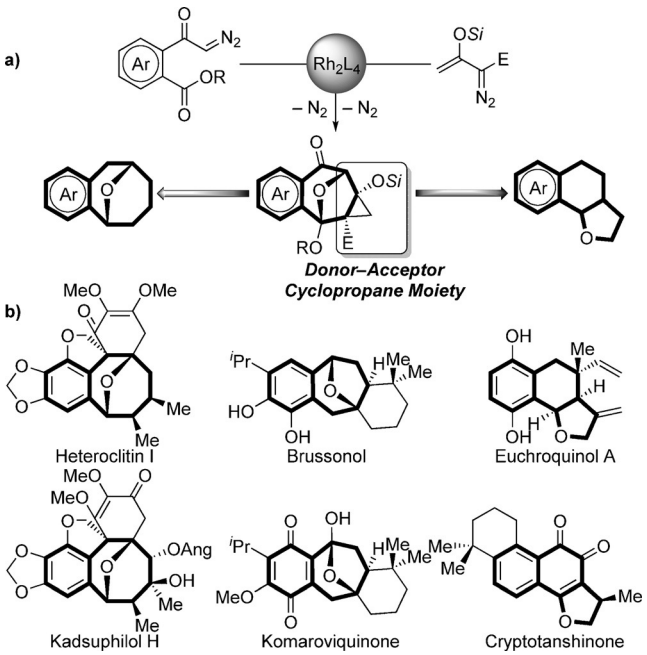
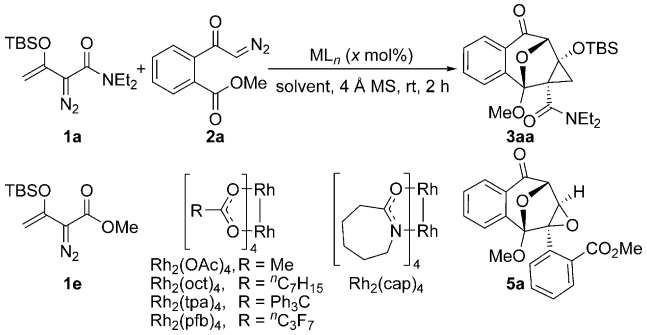


Scheme 2. a) Construction of fused and bridged ring systems from diazo compounds. b) Selected examples of natural products. Ang = angeloyl.

Table 1: Transition-metal-catalyzed annulation of enoldiazo compounds **1** with α-diazoketone **2a**: Optimization of reaction conditions.[a]



Entry	ML$_n$	x	Solvent	Yield of **3** [%][b]	*exo*:*endo* of **3**[c]	Yield of **5a** [%][b]
1	Rh$_2$(OAc)$_4$	2	$CHCl_3$	56	5:1	31
2	Rh$_2$(oct)$_4$	2	$CHCl_3$	36	16:1	54
3	Rh$_2$(tpa)$_4$	2	$CHCl_3$	33	>20:1	44
4	Rh$_2$(cap)$_4$	2	$CHCl_3$	35	>20:1	42
5	Rh$_2$(pfb)$_4$	2	$CHCl_3$	80	>20:1	<5
6	Rh$_2$(pfb)$_4$	1	$CHCl_3$	72	>20:1	9
7	Rh$_2$(pfb)$_4$	2	CH_2Cl_2	74	>20:1	<5
8	Rh$_2$(pfb)$_4$	2	DCE	71	>20:1	<5
9	Rh$_2$(pfb)$_4$	2	toluene	78	>20:1	10
10	Rh$_2$(pfb)$_4$	2	THF	52	10:1	<5
11[d]	Rh$_2$(pfb)$_4$	2	$CHCl_3$	14	n.d.	32
12	Cu(MeCN)$_4$BF$_4$	10	$CHCl_3$	9	n.d.	16

[a] Reaction conditions: ML$_n$/**1a**/**2a** = 0.002*x*:0.3:0.2 (mmol), with 4 Å molecular sieves (50 mg) in specified solvent (2 mL) at room temperature for 2 h. [b] Isolated yields after flash column chromatography. [c] Ratios were determined by ^{1}H NMR analysis of the reaction mixtures. [d] Enoldiazoacetate **1e** was used instead of enoldiazoacetamide **1a**. n.d. = not detected.

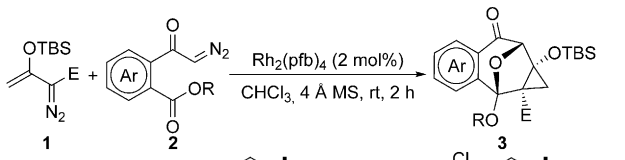
competing reaction (entry 1).[7] By contrast, rhodium(II) octanoate [Rh$_2$(oct)$_4$] was unfavorable in terms of cross-selectivity, providing a 2:3 ratio between **3aa** and dimeric product **5a** (entry 2). Rhodium(II) triphenylacetate [Rh$_2$(tpa)$_4$] and rhodium(II) caprolactamate [Rh$_2$(cap)$_4$] both gave results similar to those obtained with Rh$_2$(oct)$_4$ (entries 3 and 4). However, rhodium(II) perfluorobutyrate [Rh$_2$(pfb)$_4$] markedly improved the efficiency of this process, affording the annulation product in 80% isolated yield with excellent cross-selectivity and complete regio- and diastereocontrol (entry 5).[8] The regio- and stereochemistry in this reaction was confirmed by X-ray diffraction (XRD) analysis of a single crystal of **3aa** (see Figure S1 in the Supporting Information).[9] It should be noted that 1 mol% of Rh$_2$(pfb)$_4$ was sufficient to produce satisfactory results (entry 6).

Alternative solvents were then examined in the annulation reaction (Table 1, entries 7–10). Dichloromethane (CH_2Cl_2), 1,2-dichloroethane (DCE), and toluene were also suitable for this transformation, albeit with slight diminutions in the yield of **3aa** (entries 7–9); whereas tetrahydrofuran (THF) significantly lowered reactivity (entry 10). Furthermore, use of other reagent or metal catalyst, namely enoldiazoacetate **1e** or copper(I) tetrafluoroborate [Cu(MeCN)$_4$BF$_4$], furnished only minor amounts of their respective annulation products (entries 11 and 12). According to our previous observations, the combination of dirhodium(II) catalysts and enoldiazoacetates,[2a–c] as well as copper(I) catalysts and enoldiazoacetamides,[2d] has proven successful in metal enolcarbene transformations, especially in [3+3]-cycloadditions; in contrast, dirhodium(II) catalysts combined with enoldiazoacetamides were poorly reactive in [3+3]-cycloaddition process,[2d] but exhibited their unique efficiency in the current system.

The aforementioned results not only define the optimal conditions, but also provide further insights into the reaction mechanism. In accord with the general process given in Scheme 1b, 1) Rh$_2$(pfb)$_4$ facilitates dinitrogen extrusion from enoldiazoacetamide **1** to form metallo-enolcarbene **I**, which then undergoes intramolecular rearrangement with elimination of the rhodium catalyst, in preference to other subsequent transformations, to generate donor-acceptor cyclopropene **4**; 2) simultaneously, carbonyl ylide **II** is formed from α-diazoketone **2** with the promotion of Rh$_2$(pfb)$_4$ and reacts preferentially with the cyclopropene over the enoldiazoacetamide or its metallo-enolcarbene; 3) importantly, cyclopropene **4** is relatively stable and accumulates in solution, whereas carbonyl ylide **II** is a transient intermediate that is trapped by the cyclopropene, rather than reacting with itself, to produce annulation product **3**.

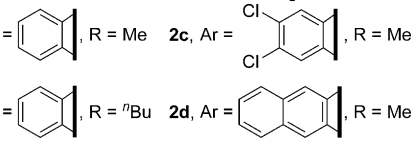
The substrate scope of this reaction was then investigated under the optimal conditions obtained with **1a** and **2a** (Table 1, entry 5), and the results are presented in Table 2. Enoldiazoacetamides bearing dialkylamino (**1a**, **1b**) and cyclic amino (**1c**, **1d**) moieties were all ideal reagents for this reaction, furnishing their respective products **3aa**–**3da** in good yields (Table 2, entries 1–4). For α-diazoketones **2**, neither changing the ester group (**2b**) nor introducing substituents onto the phenyl ring (**2c**) affected the efficiency of this process (entries 5–8). Also, α-diazoketone **2d** that

Table 2: Dirhodium(II)-catalyzed annulation of enoldiazoacetamides **1** with α-diazoketones **2**: Substrate scope.[a]



1 **2** **3**

1a, E = $CONEt_2$
1b, E = $CONMe_2$
1c, E = $CON(CH_2)_5$
1d, E = $CON(CH_2)_4$

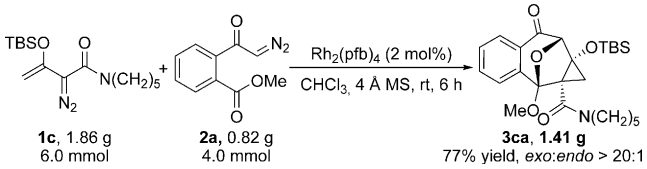


Entry	Diazo **1**	Diazo **2**	Product	Yield [%][b]	*exo*:*endo*[c]
1	**1a**	**2a**	**3aa**	80	>20:1
2	**1b**	**2a**	**3ba**	76	>20:1
3	**1c**	**2a**	**3ca**	81	>20:1
4	**1d**	**2a**	**3da**	78	>20:1
5	**1a**	**2b**	**3ab**	79	>20:1
6	**1c**	**2b**	**3cb**	82	>20:1
7	**1a**	**2c**	**3ac**	76	>20:1
8	**1c**	**2c**	**3cc**	84	>20:1
9	**1a**	**2d**	**3ad**	51	>20:1
10	**1c**	**2d**	**3cd**	62	>20:1

[a] Reaction conditions: $Rh_2(pfb)_4$/**1**/**2** = 0.004:0.3:0.2 (mmol), with 4 Å molecular sieves (50 mg) in chloroform (2 mL) at room temperature for 2 h. [b] Isolated yields after flash column chromatography. [c] Ratios were determined by ^1H NMR analysis of the reaction mixtures.

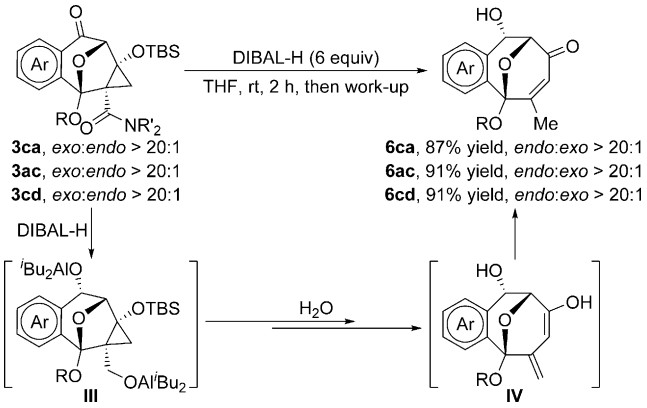
carries a naphthyl ring smoothly underwent reactions to afford the desired annulation products, albeit with moderate yields (entries 9 and 10). Remarkably, exceptional regio- and diastereoselectivities were achieved in all the cases: no regio- or diastereoisomers of products **3** were detected in the reaction mixtures.

To demonstrate the reliability and practicality of the present synthetic methodology, a gram-scale experiment was carried out with diazo compounds **1c** and **2a**, affording 1.41 g of product **3ca** in good yield with complete regio- and diastereocontrol (Scheme 3). It is worth mentioning that the annulation product is an easily handled solid, which showed no change in open air over three months.



Scheme 3. Gram-scale synthesis. See Section 3 of the Supporting Information for reaction details.

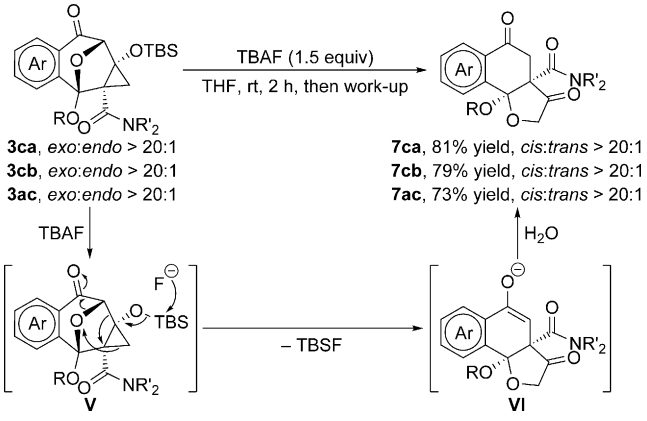
Intrigued with these unique products that bear highly strained donor–acceptor cyclopropane moieties, we further explored their transformations in the presence of simple, commercially available reagents. After treating annulation products **3** with diisobutylaluminium hydride (DIBAL-H), benzoxa[3.3.1]nonane derivatives **6** were formed in high yields with exact stereocontrol (Scheme 4). The relative



Scheme 4. Stereospecific transformation of annulation products **3** into benzoxa[3.3.1]nonane derivatives **6**. See Section 4 of the Supporting Information for reaction details.

configuration of **6ca**, and others in this series by analogy, was determined by single-crystal XRD analysis (see Figure S2 in the Supporting Information).[9] Additionally, replacement of DIBAL-H with $LiAlH_4$ afforded identical products with slightly diminished yields.[10] As depicted in Scheme 4, we suggest **IV** as a possible intermediate, which is generated through a ketone and amide reduction/cyclopropane opening/TBS and hydroxy elimination process and produces **6** via a following [1,5]-hydrogen shift.

Furthermore, an unprecedented rearrangement of **3ca** was induced by tetra-*n*-butylammonium fluoride (TBAF), furnishing hexahydronaphthofuran derivative **7ca** as a single diastereomer in 81% yield (Scheme 5). Other tested annulation products **3cb** and **3ac** also performed well in this transformation. The structure and stereochemistry of the rearrangement products were confirmed by X-ray crystallographic analysis of **7ac** (see Figure S3 in the Supporting Information).[9] A plausible rearrangement pathway is proposed and illustrated in Scheme 5. Annulation product **3** undergoes intramolecular electron transfer triggered by fluoride-promoted removal of the TBS group, in a concerted or stepwise fashion, to generate intermediate **VI**; and



Scheme 5. Stereospecific transformation of annulation products **3** into hexahydronaphthofuran derivatives **7**. See Section 5 of the Supporting Information for reaction details. TBSF = *tert*-butyldimethylsilyl fluoride.

subsequent protonation followed by enol–keto tautomerism completes the transformation.

In summary, by adding the mixture of two easily accessible diazocarbonyl compounds to a commercially available dirhodium catalyst, four C–C or C–O bonds, along with three fused or bridged rings, were formed in a highly chemo-, regio-, and diastereoselective manner under exceptionally mild conditions. The employment of $Rh_2(pfb)_4$ and enoldiazoacetamides is crucial for achieving compatible reactivity and controllable selectivity in this reaction. Furthermore, in the presence of simple, commercially available reagents, the donor–acceptor cyclopropane-fused benzoxa[3.2.1]octane products can be readily transformed into benzoxa[3.3.1]nonane and hexahydronaphthofuran derivatives with exact stereocontrol. This method utilizes two structurally different diazo compounds to efficiently construct three natural product-related ring systems, which may open up new possibilities for the application of diazo compounds in organic synthesis.

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[8] Neither carbonyl ylide dimer **5a** nor regio- and diastereoisomers of **3aa** were detected in the reaction mixture.

[9] CCDC 1426298 (**3aa**), 1433609 (**6ca**), and 1447179 (**7ac**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[10] For more details, see Section 4 of the Supporting Information.

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