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Rhodium(II) catalyzed intermolecular double C-alkylation: a method for the synthesis of tetraindoles and indolophanes

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ABSTRACT

Double C-alkylation of cyclic diazoamides or bis-diazoamides with indoles or bis-indoles has been achieved to synthesize tetraindole derivatives using rhodium(II) acetate as a catalyst under mild reaction conditions with complete regioselectivity. The intermolecular double C-alkylation reaction strategy was successfully applied to synthesize indolophanes in moderate yield with excellent regiocontrol. The structure and stereochemistry of macrocycles were unequivocally confirmed with the help of single-crystal X-ray structure analyses.

1. Introduction

Plethora of reports are available, in which 'rhodium(II) catalysts' were highly selective for transformations, such as cyclopropanation, insertion, and ylide formation.[1] Interesting developments were seen in the past few years, particularly, the combination of transition metal-catalyzed cyclopropanation followed by other types of reactions in a single or cascade operation. Owing to the high strain of the three-membered ring system, there are many possible pathways for the ring opening of cyclopropanes. Cyclopropane rings bearing both electron-donating and -withdrawing groups are prone to undergo ring opening[2] reactions. The reactions of metallo-carbenoids with furan,[3] pyrrole[4] or indole[4] resulted in an initial cyclopropanation followed by a consecutive ring opening process. Similarly, cyclopropanation of other heterocycles including activated quinolines, isoquinolines,[5] and benzopyrylium triflates,[6] followed by the ring enlargement reaction was also reported. Many indoline alkaloids[7] were synthesized via cyclopropanation followed by ring opening strategy. The rhodium-catalyzed intramolecular reactions of pyrrolyl and indolyl diazoketones generally resulted[8] in the alkylation products via cyclopropanation. Conversely, the inter- as well as intramolecular reactions of diazo compounds with indole in the presence of copper catalysts afforded the corresponding cyclopropanation[5,9] across the indole 2,3-double bond. Our recent report indicates that the reactions of metallo-carbenoids derived from diazoamides **1** with heteroaromatic systems, such as benzofuran and benzothiophene afforded[10] the cyclopropanation products without any ring opening. However, reaction of cyclic diazoamide **1** (R^1=Me) with *N*-benzylindole **2** (R^2=Bn) in the presence of $Rh_2(OAc)_4$ afforded the corresponding 3-alkylated product[11] **5** in quantitative yields with the complete regioselectivity (Scheme 1). This process reveals that the formation of product **5** might be produced via the corresponding spirocyclopropanes **3** and followed by ring opening to zwitterions **4** as intermediate in the presence of copper or rhodium catalyst.

The design and synthesis of macrocycles containing aromatic/heteroaromatic ring systems are an intriguing branch of organic and supramolecular chemistry.[12,13] However, aromatic units present in the cyclophanes are mostly carbocyclic rings, such as benzene or naphthalene derivatives. Our enticement in developing a new synthetic strategies[14] using diazocarbonyl compounds encouraged us to investigate the application of the cyclopropane/ring opening methodology for the synthesis of indolophanes (Scheme 2). We herein report the intermolecular double C-alkylation reactions of cyclic diazoamides **6** in the presence of $Rh_2(OAc)_4$ catalyst in a single synthetic step furnishing tetraindole derivatives (indolophanes) with excellent regiocontrol via cyclopropanation followed by ring opening process.

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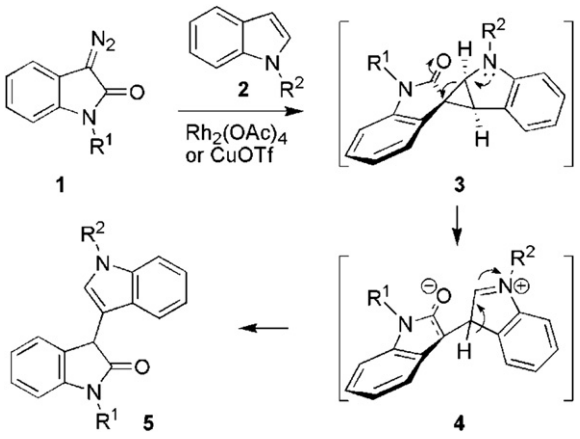
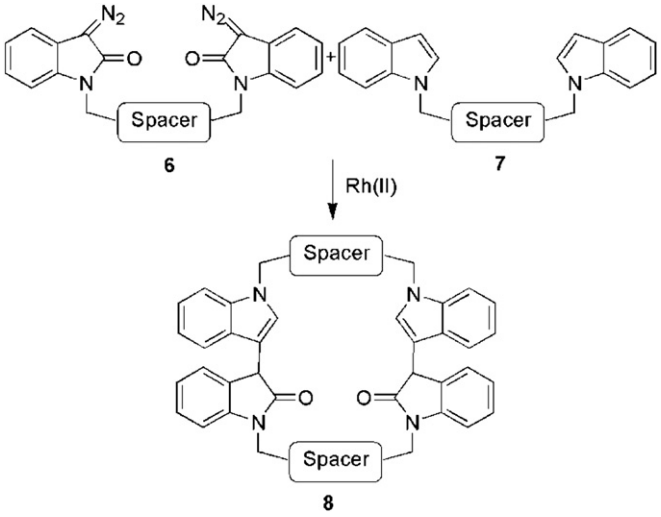


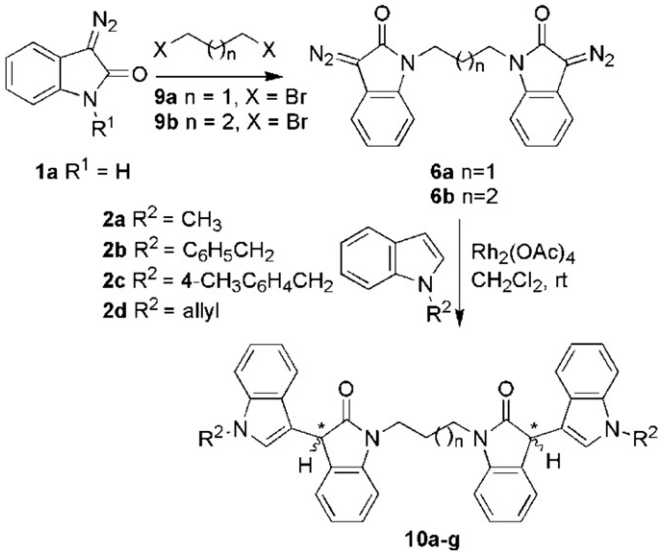
Scheme 1. Synthesis of 3-alkylated product **5**.



Scheme 2. Synthesis of indolophanes.

2. Results and discussion

With an objective to synthesize macrocycles utilizing rhodium(II) carbenoids, the selection of spacers was initially planned to interconnect the indole and diazoamide units that provide flexibility with respect to the ring size and the kind of structural units to be incorporated in the macrocycles. Based on our earlier research work[10,11,14b] on C-alkylation, we designed the double intermolecular C-alkylation reactions of bis-diazoamides **6** with indoles **2** or bis-indoles **7**. To demonstrate the double C-alkylation reaction, bis-diazoamides **6a**,**b** having aliphatic spacers were synthesized in good yield via N-alkylation of diazoamide **1a** with 1,3-dibromopropane (**9a**) or 1,4-dibromobutane (**9b**) using K_2CO_3/DMF. The double C-alkylation reaction of bis-diazoamides **6a**,**b** was investigated to determine the course of reaction. Treatment of **6a** with an excess amount of *N*-methylindole **2a** in the presence of 1 mol % of rhodium(II) acetate catalyst for 20 min at room temperature furnished the corresponding double *C*-alkylated product **10a** in 85% yield as a mixture of diastereomers in the ratio of 1:1 (Scheme 3). No mono-alkylated product was observed. The ^{1}H NMR spectrum of compound **10a** exhibited a characteristic signal at δ 4.81 and 4.85 as two separate singlets for two C*–H protons of each diastereomer. Similarly, reaction of bis-diazoamides **6a**,**b** with substituted indoles **2a**–**d** furnished the corresponding double-alkylated products **10b**–**g** as a diastereomeric mixture in very good yield and the results are delineated in Table 1.



Scheme 3. Synthesis of tetraindoles from cyclic diazoamides **6**.

Table 1
Reaction of bis-diazoamides **6** with substituted indoles **2**

Entry	Product	*n*	R^2	Time (min)	Yield[a] %	dr[b]
1	**10a**	1	CH_3	20	85	59:41
2	**10b**	1	$C_6H_5CH_2$	20	93	56:44
3	**10c**	1	4-$CH_3C_6H_4CH_2$	30	82	58:42
4	**10d**	2	CH_3	15	89	65:35
5	**10e**	2	$C_6H_5CH_2$	15	89	61:39
6	**10f**	2	4-$CH_3C_6H_4CH_2$	15	77	59:41
7	**10g**	2	Allyl	20	80	60:40

[a] Isolated yield.
[b] Diastereomeric ratio based on the crude NMR spectra.

Having studied the reaction profile of bis-diazoamides, we next examined the double C-alkylation reaction of bis-indoles **7** with cyclic diazoamides **1b**–**f**. Thus, reaction of bis-indole **7a** with an excess amount of cyclic diazoamide **1b** in the presence of 1 mol % of rhodium(II) acetate catalyst at room temperature was performed. The reaction was completed in 25 min; concentrated and chromatographic purification of the reaction mixture delivered the tetraindole derivative **11a** as a mixture of diastereomers in quantitative yields (Scheme 4). The ^{1}H NMR spectrum of product **11a** exhibited a characteristic signal at δ 4.87 as a singlet for two C*–H protons, which indicates the presence of symmetry.

The NMR spectrum showed the complete symmetry for other protons as well as carbons because the stereocenters present in diastereomers are well separated. Thus, the diastereomeric ratio could not be determined. Spectroscopic analyses confirmed the double C-alkylation reaction of bis-indoles with complete regioselectivity. Similarly, the reaction of bis-indoles **7a**,**b** with substituted cyclic diazoamides **1b**–**f** furnished the corresponding double-alkylated products **11b**–**j** as a mixture of diastereomers in quantitative yield and the results are delineated in Table 2.

Next, double alkylation reactions of bis-indoles **7** having aromatic spacers were planned to furnish tetraindole derivatives. Reaction of bis-indole containing aromatic spacer **7c** with cyclic diazoamide **1b** afforded the alkylated product **12a** as a mixture of diastereomers (Scheme 5). However, ^{1}H NMR spectrum of product **12a** exhibited a characteristic singlet resonance at δ 4.86 for two