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A Highly Diastereo- and Enantioselective Hg(II)-Catalyzed Cyclopropanation of Diazooxindoles and Alkenes

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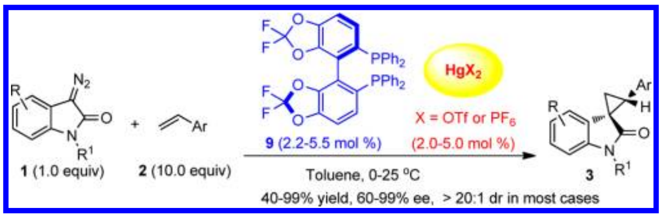
ABSTRACT



It is reported for the first time that Hg(II) can catalyze the cyclopropanation of diazo reagents and alkenes, which contributes to the unprecedented highly diastereo- and enantioselective synthesis of spirocyclopropyloxindoles.

The metal-catalyzed cyclopropanation between diazo compounds and alkenes is a powerful strategy for the synthesis of cyclopropane derivatives.[1] Despite that, the search for stereoselective catalysts has a long and continuing history,[2–6] and there is still much work to to be done to enable diazo compounds with low reactivity and poor stereocontrollability for catalytic asymmetric reactions. For example, catalytic asymmetric synthesis of spirocyclic compounds using cyclic diazoamides such as diazooxindoles **1** is unprecedented, although spirocyclopropyl oxindoles **3** are very vaulable, which are known to have inotropic and herbicidal properties.[7] Furthermore, Carreira et al. have demonstrated that oxindole **3** is a

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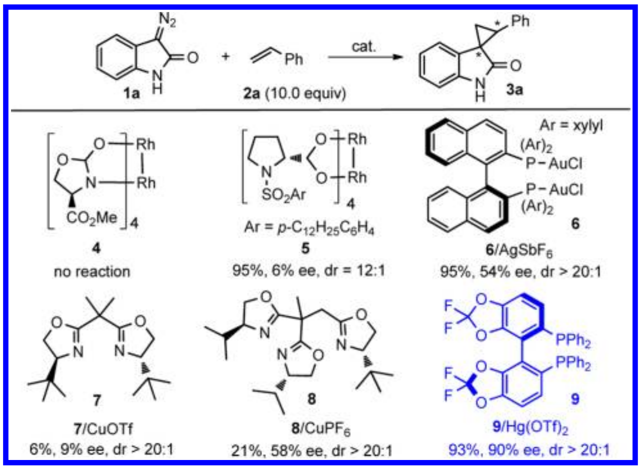
versatile synthon for the synthesis of spiro[pyrrolidin-3,3′-oxindoles] via the ring-expansion reaction with imines.[8] Recently, the need for privileged scaffolds in drug discovery gives an impetus for the catalytic asymmetric synthesis of 3,3-disubstituted oxindoles, which are widely present in natural products and drugs.[9,10] With our interest in this field,[11] we tried to apply diazooxindoles **1** for catalytic asymmetric reactions and found that although catalysts **4**−**8**[3a,3c,12,2c,2e] had proven to be excellent for the decomposition of diazo compounds for reaction design, they were unable to achieve high ee in the reaction of diazoamide **1a** and styrene **2a** under their reported conditions, respectively (Scheme 1, for details, see the Supporting Information). These results showed the necessity to develop new chiral catalysts for this valuable reaction. Here, we report a Hg(II)-catalyzed highly enantioselective reaction of diazooxindoles **1** and alkenes **2**.

Scheme 1. Exploratory Studies



We have reported that Hg(II) could highly efficiently activate allyltrimethylsilane for allylation of isatins and activate electron-rich aromatics for the arylation of 3-hydroxyoxindoles.[13] Considering the excellence of Hg(II) as a soft Lewis acid to activate soft bases, we speculated that it would be possible to use Hg(II) to decompose diazo compounds, a kind of soft bases,[14] for cyclopropanation reactions. With this in mind, we tried using 5.0 mol % of $Hg(OTf)_2$ to catalyze the reaction of **1a** and **2a** in CH_2Cl_2 at 0 °C and found to our delight that the reaction could be complete within 4 h to give product **3a** in 60% yield with excellent dr (entry 1, Table 1). We further compared $Hg(OTf)_2$ with other widely used metal catalysts in this reaction, and $Hg(OTf)_2$ turned out to be more efficient (entries 2−10). $Rh_2(OAc)_4$ failed to catalyze the reaction at 0 °C but worked well at 25 °C to give product **3a** in 91% yield after 48 h, with lower dr (entry 2). Even at 25 °C, Ru(II), Cu(I), and Cu(II) catalyzed the reaction very slowly (entries 3−5). At 0 °C, $Pd(OTf)_2$ catalyzed the reaction at a much lower rate than $Hg(OTf)_2$ (entry 6 vs 1). Other triflates derived from Ag(I), Co(II), Fe(III), and Fe(II) all failed to catalyze this reaction, either at 0 or 25 °C (entries 7−10). These results were in accordance with Wang's observation that the reactivity of diazooxindole **1** was low.[7d]

The high efficiency that $Hg(OTf)_2$ demonstrated in this reaction was very impressive, which encouraged us to develop an asymmetric protocol. Diphosphine ligands could effectively modulate the catalyst properties of $Hg(OTf)_2$,

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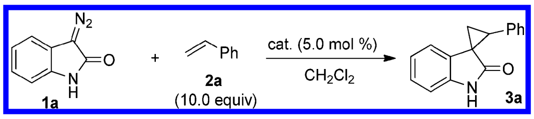
Table 1. Comparing Different Metal Salts[a]

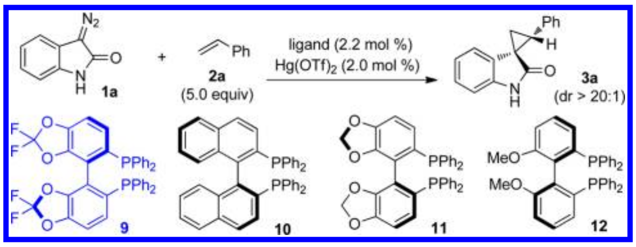


entry	cat.	temp (°C)	time (h)	yield[b] (%)	dr[c]
1	$Hg(OTf)_2$	0	4	60	>20:1
2	$Rh_2(OAc)_4$[d]	0 (25)	24 (48)	nr[g] (91)	nd[g] (13:1)
3	$(Ph_3P)_3Ru(OTf)_2$	0 (25)	24 (48)	nr (30)	nd (10:1)
4	$CuOTf\cdot 1/2C_6H_6$	0 (25)	24 (48)	nr (30)[e]	nd (20:1)
5	$Cu(OTf)_2$	0 (25)	24 (48)	nr (31)[e]	nd (20:1)
6	$Pd(OTf)_2$[f]	0	24	39[e]	>20:1
7	AgOTf	0 (25)	24 (48)	nr	nd
8	$Co(OTf)_2$[f]	0 (25)	24 (48)	nr	nd
9	$Fe(OTf)_3$	0 (25)	24 (48)	nr	nd
10	$Fe(OTf)_2$	0 (25)	24 (48)	nr	nd

[a] On a 0.20 mmol scale. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] 2.5 mol %. [e] NMR yield using 1,3,5-$Me_3C_6H_3$ as the internal standard. [f] By anion exchange of $PdCl_2$ or $CoCl_2$ with AgOTf. [g] nr = no reaction. nd = not determined.

and the electron-deficient ligand (*R*)-**9**[15] proved to be the best, which afforded product **3a** in 62% yield and 61% ee (Table 2, entries 1−4). Further screening revealed that toluene was the optimal reaction solvent (entry 5). When the reaction was run at 0 °C, using 5 mol % of chiral catalyst **9**/$Hg(OTf)_2$ and 10.0 equivs of styrene **2a**, up to 90% ee and 93% yield for product **3a** was achieved (entry 6). For the full studies of condition optimization, see the Supporting Information.

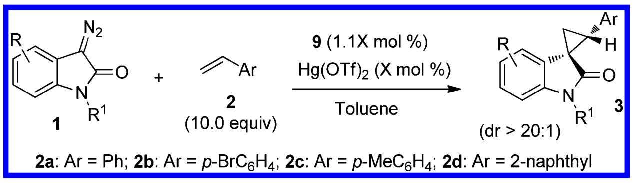
Table 2. Condition Optimization[a]



entry	L	solvent	temp (°C)	time (h)	yield[b] (%)	ee (%)
1	**9**	CH_2Cl_2	25	1	62	61
2	**10**	CH_2Cl_2	25	2	52[c]	45[c]
3	**11**	CH_2Cl_2	25	24	49[c]	51[c]
4	**12**	CH_2Cl_2	25	4	71	49
5	**9**	toluene	25	5	64	87
6[d]	**9**	toluene	0	12	93	90

[a] On a 0.20 mmol scale. [b] Isolated yield. [c] Opposite enantiomer. [d] 5.5 mol % of **9**, 5.0 mol % of $Hg(OTf)_2$, and 10.0 equiv of **2a** used.

Table 3. Substrate Scope[a]



entry	1	2	X	temp (°C)	3	yield[b] (%)	ee[c] (%)
1	**1a**: R = H, R^1 = H	**2a**	5	0	**3a**	93	90
2	**1b**: R = H, R^1 = Me	**2a**	5	0	**3b**	82	94
3	**1c**: R = H, R^1 = Bn	**2a**	5	0	**3c**	58	91
4	**1d**: R = 5-Me, R^1 = H	**2a**	5	0	**3d**	89	87
5	**1e**: R = 7-Me, R^1 = H	**2a**	5	0	**3e**	78	93
6	**1f**: R = 5,7-Me_2, R^1 = H	**2a**	5	0	**3f**	97	90
7	**1g**: R = 6,7-Me_2, R^1 = H	**2a**	5	0	**3g**	92	91
8	**1h**: R = 4,6-Me_2, R^1 = H	**2a**	2	25	**3h**	84	99
9	**1i**: R = 5-F, R^1 = Me	**2a**	2	25	**3i**	87	90
10	**1j**: R = 5-Cl, R^1 = Me	**2a**	2	25	**3j**	90	87
11	**1k**: R = 5-Br, R^1 = H	**2a**	2	25	**3k**	97	83
12	**1l**: R = 5-I, R^1 = Me	**2a**	2	25	**3l**	90	90
13	**1m**: R = 7-Cl, R^1 = Me	**2a**	2	25	**3m**	93	92
14	**1b**: R = H, R^1 = Me	**2b**	2	25	**3n**	99	92
15[d]	**1a**: R = H, R^1 = H	**2c**	5	0	**3o**	57	86
16	**1a**: R = H, R^1 = H	**2d**	5	0	**3p**	48	86

[a] On a 0.20 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 13:1 dr.

The substrate scope with respect to different diazooxindoles **1** and alkenes **2** was then examined (Table 3). Generally, the nature and position of substituent on the diazooxindoles had no big influence on the enantiofacial control, and diazooxindoles **1a**−**m** afforded the desired products **3a**−**m** in high to excellent ee (entries 1−13). Other aromatic substituted alkenes **2b**−**d** also worked well to give the desired products **3n**−**p** in reasonable yield with high ee (entries 14−16). The absolute configuration of product **3n** was determined by X-ray analysis (Figure 1), and those of others were tentatively assigned by analogy.

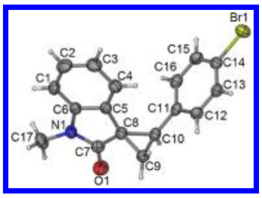


Figure 1. X-ray structure of product **3n**.

The less reactive disubstituted alkenes were also viable substrates for this reaction, if the counteranion was changed from OTf^- to PF_6^-. Accordingly, when 5.0 mol % of in situ generated catalyst **9**/$Hg(PF_6)_2$ was used, α-methylstyrene **2e** provided product **3q**, with two adjacent quaternary stereogenic carbon centers, in excellent dr and 83% ee. While a trans double bond is generally deemed to be too sterically

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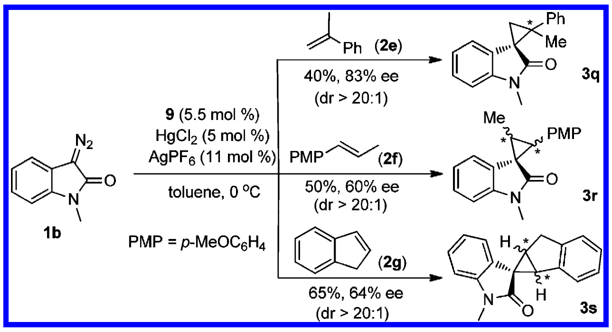
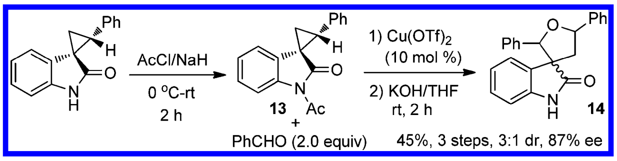
crowded for cyclopropanation,[16] the *trans*-anethole **2f** could give the desired product **3r** in 50% yield, excellent dr, and 60% ee under these improved conditions. The diazooxindole **1b** could react with indene **2g** to give strained spirocyclopropanooxindole **3s** in excellent dr, 65% yield, and 64% ee.

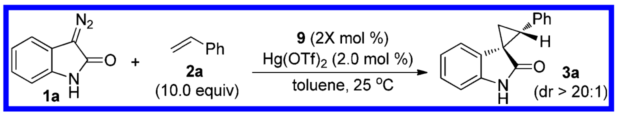


The synthetic utility of the spirocyclopropyl oxindoles **3** was shown by an unprecedented [3 + 2] cycloaddition of spirocyclopropyl oxindoles **3** with aldehyde. After protection, the resulting *N*-acetyloxindole **13** could react with benzaldehyde, in the presence of 10 mol % of Cu(OTf)$_2$, to furnish spiro[furan-3,3′-indolin]-2-one **14** in 45% overall yield for three steps, 3:1 dr and 87% ee. This transformation might have potential application in the synthesis of spirocyclic oxindoles of current interest.[9,10]



While Corma recently mentioned that “there is not a single example of a ligand-modulated Hg(II) catalyst”,[17] the results shown above clearly demonstrated that the catalyst properties of Hg(II) could be readily modulated by variation of ligands and counteranions. Furthermore, this cyclopropanation reaction turned out to be ligand-accelerated. Without ligand **9**, the reaction proceeded very slowly in toluene at 25 °C, and only 7% of **3a** was obtained after 18 h (entry 1, Table 4). In sharp contrast, the use of only 0.1 equiv of ligand **9** relative to Hg(OTf)$_2$ dramatically improved the reactivity, and product **3a** was obtained in 74% yield with 83% ee (entry 2). This result confirmed that the property of Hg(II) could be modulated by using diphosphine ligands, which offers the promise to develop more powerful chiral mercury catalysts. Currently, the reaction mechanism is under investigation.

Table 4. Ligand Acceleration Studies[a]



entry	X	time (h)	yield[b] (%)	ee[c] (%)
1	0	18	7	nd
2	0.1	5	74	83
3	0.2	5	77	83
4	0.4	5	82	86
5	0.5	5	83	87
6	1.1	5	89	87

[a] On a 0.20 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Although the chiral catalytic species was under investigation, the high dr observed in this Hg(II)-catalyzed reaction could be rationalized by the general model, proposed by Davies,[3d] for cyclopropanation involving donor/acceptor carbenoids. The alkene approached the carbenoid intermediate side-on over the lactam group, with the Ar group of the alkene favoring an orientation away from the bulky metal (Figure 2), which finally led to the formation of *trans* isomer as the major product.

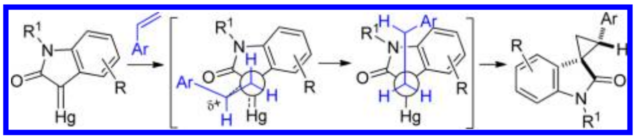


Figure 2

In conclusion, we have discovered that Hg(II) could catalyze the cyclopropanation of diazo reagents and alkenes, which rebounds to the first highly diastereo- and enantioselective synthesis of spirocyclopropyl oxindoles from diazooxindoles and alkenes. We also proved that the catalytic properties of Hg(II) could be readily modulated by variation of ligands and counteranions. Considering the high efficiency that Hg(II) exhibited in this useful reaction, we believe that mercury compounds might find more applications in asymmetric catalysis.[18,19]

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Supporting Information Available. Experimental procedures and characterizations, copies of ^{1}H NMR and ^{13}C NMR of new compounds, and HPLC profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Caution: Special care should be taken when using mercury salts and disposing of the waste containing mercury due to the toxicity of mercury salts.

The authors declare no competing financial interest.