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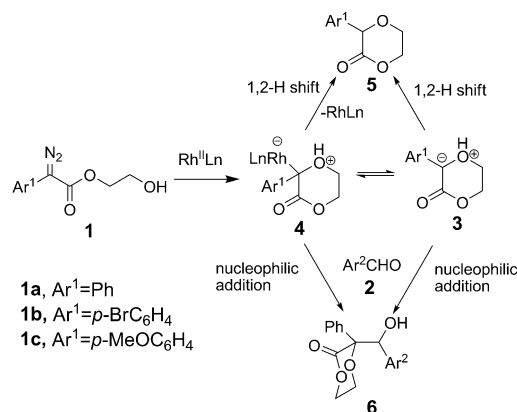
A Facile Access to Polyfunctional Oxygen-containing Heterocycles via Intramolecularly Formed Protic Oxonium Ylide Trapping Processes

Xin Guo, Wei Liu, and Wenhao Hu*^[a]

Abstract: Based on the assumption that intramolecularly formed protic oxonium ylides could be trapped by electrophiles, transition-metal-catalyzed reactions of diazoesters bearing a primary hydroxy group with electron-deficient aldehydes and isatins were examined. Good to high chemo- and diastereoselectivities were achieved with reactions catalyzed by Cu(hfacac)₂. The reactions were assumed to occur via tandem intramolecular protic oxonium ylide formation and subsequent aldol-type addition. They not only provided an efficient entry to 3-substituted 1,4-dioxan-2-one heterocycles with at least one quaternary carbon center but also provided experimental evidence for a stepwise pathway for the transition-metal-catalyzed intramolecular O–H insertion of diazo compounds.

Due to the advantages of atom efficiency and ease of implementation, tandem reactions have received considerable attention for the rapid generation of complex and diverse molecules.^[1] Tandem processes involving metallo carbenoids and onium ylide intermediates have been applied in organic synthesis. For example, tandem carbonyl ylide formation and 1,3-dipolar cycloaddition sequences have an inherent advantage in assembling polycyclic structures.^[2] A similar tandem process involving intramolecular ethereal or thioetheral ylide formation and subsequent intermolecular carbon–carbon bond formation was also reported to afford medium-sized oxygen/sulfur-containing rings with a β -hydroxy alkyl ether moiety.^[3] Recently, we have uncovered a series of novel three-component reactions, in which protic oxonium ylides, generated in situ from carbenoids and alcohols or water, underwent nucleophilic addition to carbonyl compounds, thereby providing a convergent synthesis of α,β -dihydroxy acid derivatives.^[4] Successful trapping of the protic oxonium ylides also provided evidence for a stepwise ylide-mediated pathway rather than a concerted one for intermolecular O–H insertions triggered by catalytic reactions of diazo compounds.

Meanwhile, intramolecular O–H insertions have also been extensively studied and offer a convenient way to construct cyclic ethers.^[5] The reaction may occur via a two-step process: 1) Formation of a protic oxonium ylide intermediate and 2) Inter- or intramolecular proton transfer. However, no direct evidence to prove such a stepwise process has been reported.^[6] Based on our previous experience in the trapping process of protic oxonium ylides, we assumed that the intramolecularly formed protic oxonium ylide may be trapped by a proper electrophile if the proton transfer is a rate-determining step in the aforementioned two-step process.^[4a] Herein, we report the first example of the tandem intramolecular formation of a protic oxonium ylide and subsequent trapping of such a ylide through an aldol-type addition with carbonyl compounds (Scheme 1). The



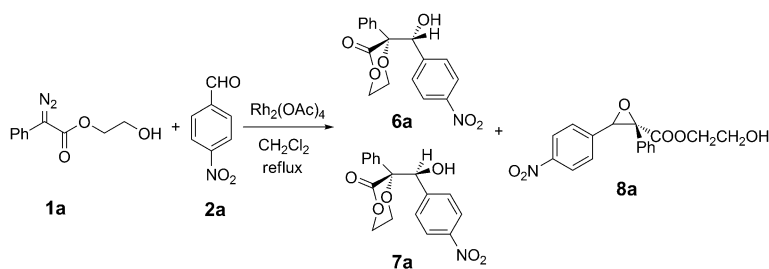
Scheme 1. Proposed reaction pathway for trapping of cyclic protic oxonium ylide.

successful trapping reaction provides an efficient entry for polyfunctional 1,4-dioxan-2-one heterocycles. The 1,4-dioxan-2-one moiety is present in many biologically active compounds such as lactonized oligosialic and polysialic acid derivatives,^[7] and it also serves as a building block for the α -hydroxy acid motif.^[8]

To study a model reaction, we designed and prepared diazoesters **1** bearing a primary hydroxy group and examined the transition-metal-catalyzed diazo decomposition of **1** in the presence of an electron-deficient aromatic aldehyde (Scheme 1).

[a] Dr. X. Guo, W. Liu, Prof. Dr. W. Hu
Shanghai Engineering Research Center of Molecular Therapeutics
and New Drug Development
East China Normal University
Shanghai 200062 (China)
E-mail: whu@chem.ecnu.edu.cn

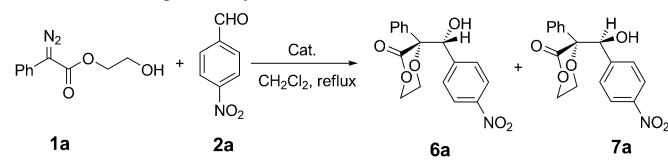
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Scheme 2. Rh(II)-catalyzed reaction of **1a** and **2a**.

Initially, $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction of **1a** was performed in refluxing CH_2Cl_2 in the presence of 4-nitrobenzaldehyde (**2a**). We were pleased to find that the expected trapping products **6a** and **7a** were obtained in 55% yield with 67:33 d.r. favoring **6a** (Scheme 2). Under such conditions, the epoxidation side product **8a** was isolated in 15% yield (Table 1, entry 1). In addition, no intramolecular O–H

Table 1. Screening of catalysts.



Entry ^[a]	Catalyst	Yield [%] ^[b]	d.r. (6a / 7a) ^[c]
1	$\text{Rh}_2(\text{OAc})_4$	40	67:33
2	CuOTf	59	51:49
3	$\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$	60	64:36
4	$\text{Cu}(\text{acac})_2$	60	62:38
5	$\text{Cu}(\text{tfacac})_2$ ^[d]	58	50:50
6	$\text{Cu}(\text{hfacac})_2$	54	71:29
7	$\text{Cu}(\text{OTf})_2$	56	52:48

[a] All reactions were carried out in refluxing CH_2Cl_2 in the presence of $\text{Rh}_2(\text{OAc})_4$ (1 mol %) or copper catalysts (10 mol %) with **1a**/**2a** = 1.2:1.0. [b] Isolated yields of (**6a** + **7a**) after chromatography based on **2a**. [c] Determined by ^1H NMR spectroscopy of crude reaction mixtures. [d] tfacac = 1,1,1-trifluoroacetyl acetate.

insertion product was observed, thus indicating that the rate of the ylide-trapping process was much faster than the 1,2-proton transfer process. The stereochemistry of **6** was established through single-crystal X-ray analysis of **6a** (Figure 1).^[9]

Copper catalysts are highly attractive for chemical synthesis from environmental and economic points of view,^[10] and

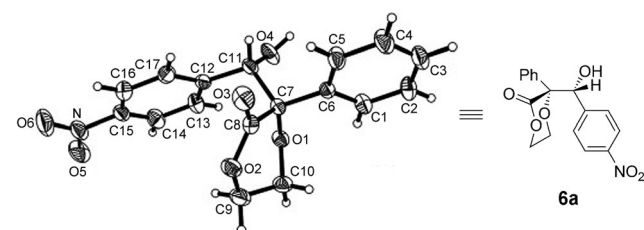


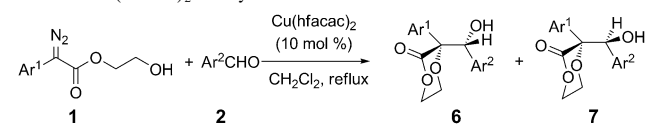
Figure 1. ORTEP illustration of **6a**.

copper complexes have shown different properties in three-component aldol or Michael-type coupling reactions.^[5e,11a,b] Several copper complexes have been investigated in the current reaction, and the results are summarized in Table 1. Generally, a slightly higher d.r. ratio of **6a**/**7a** was achieved as compared with that from the use of $\text{Rh}_2(\text{OAc})_4$, and the O–H inser-

tion product **5a** and epoxidation product **8a** were not observed. The diastereoselectivity of the reaction varied when copper catalysts were used. $\text{Cu}(\text{hfacac})_2$ (hfacac = 1,1,1,5,5,5-hexafluoroacetyl acetate) resulted in the highest d.r. (71:29 d.r.) among the catalysts used (Table 1, entry 6).

The trapping process was found to be sensitive to the electronic feature of aromatic aldehydes and the diazo compounds. Electron-deficient aromatic aldehydes gave the desired products in moderate to good yield with high diastereoselectivity (Table 2, entries 1–3). No desired three-com-

Table 2. $\text{Cu}(\text{hfacac})_2$ -catalyzed reaction of **1** and **2**.



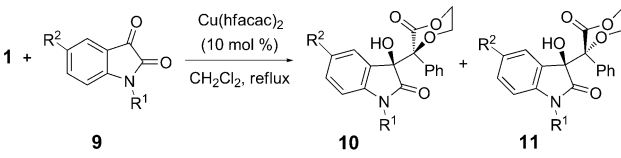
Entry ^[a]	1	2	Yield (6 + 7) ^[b]	d.r. (6 / 7) ^[c]
1	1a	<i>p</i> - $\text{CF}_3\text{C}_6\text{H}_4$	61 (6b + 7b)	93:7
2	1a	<i>p</i> - CNC_6H_4	60 (6c + 7c)	91:9
3	1a	2,4-(NO_2) $_2\text{C}_6\text{H}_3$	80 (6d + 7d)	90:10
4	1a	<i>p</i> - MeOC_6H_4	–	–
5	1b	<i>p</i> - $\text{NO}_2\text{C}_6\text{H}_4$	70 (6e + 7e)	92:8
6	1c	<i>p</i> - $\text{NO}_2\text{C}_6\text{H}_4$	–	–

[a] All reactions were carried out in refluxing CH_2Cl_2 in the presence of $\text{Cu}(\text{hfacac})_2$ (10 mol %) with **1a**/**2a** = 1.2:1.0. [b] Isolated yields of (**6a** + **7a**) after chromatography based on **2a**. [c] Determined by ^1H NMR spectroscopy of crude reaction mixtures.

ponent trapping product was obtained with electron-rich aromatic aldehydes and aliphatic aldehydes. The reaction of the bromo-substituted **1b** gave **6g**/**7g** in 70% isolated yield with 92:8 d.r. (Table 2, entry 5). However, electron-rich diazo compound **1c** gave no desired trapping product (Table 2, entry 6).

Isatins have been reported to be highly reactive electrophiles to trap protic oxonium ylides with excellent chemo- and diastereoselectivity.^[4c] Trapping of the intramolecularly formed cyclic protic ylide with isatins would produce frameworks containing both the 3-substituted 1,4-dioxan-2-one and 3-substituted 3-hydroxyindolin-2-one moieties with adjacent quaternary carbon centers, the latter of which was found in a number of biologically active alkaloids.^[12] Initially, the reaction of **1a** with *N*-methyl isatin (**9a**) was surveyed. Copper catalysts led to a higher diastereoselective

Table 3. Cu(hfacac)₂-catalyzed reaction of **1** and **9**.



Entry ^[a]	1	R ¹	R ²	Yield [%] ^[b]	d.r. ^[c]
1 ^[d]	1a	Me	H	60 (10a + 11a)	75:25
2	1a	Me	H	74 (10a + 11a)	95:5
3	1a	Ph	H	76 (10b + 11b)	95:5
4	1a	Ac	H	87 (10c + 11c)	59:41
5	1a	H	H	—	—
6	1a	Me	Br	91 (10d + 11d)	98:2
7	1a	Me	Cl	89 (10e + 11e)	96:4
8	1a	Me	F	85 (10f + 11f)	98:2
9	1a	Me	NO ₂	92 (10g + 11g)	95:5
10	1b	Me	NO ₂	92 (10h + 11h)	93:7
11	1c	Me	NO ₂	—	—

[a] All reactions were carried out in refluxing CH₂Cl₂ in the presence of Cu(hfacac)₂ (10 mol %) with **1**/**9** = 1.2:1.0. [b] Isolated yields of (**10** + **11**) after chromatography based on **9**. [c] Determined by ¹H NMR spectroscopy of crude reaction mixtures. [d] In the presence of Rh₂(OAc)₄ (1 mol %).

control of the ylide-trapping process than Rh₂(OAc)₄ (Table 3, entry 1). Again, Cu(hfacac)₂ gave the highest yield (74 %) and diastereoselectivity (95:5 d.r.) (Table 3, entry 2). A number of substituted isatins were then used in the reaction with **1a**. *N*-phenyl isatin gave a similar yield and diastereoselectivity, while *N*-acetyl isatin gave a higher yield but lower diastereoselectivity (Table 3, entries 3 and 4). No addition product was observed from the reaction of **1a** and *N*-H isatin, and a significant amount of **1a** was recovered (Table 3, entry 5). We assumed that the catalyst Cu(hfacac)₂ was poisoned by the *N*-H isatin and lost its catalytic activity for the diazo decomposition. When 5-substituted *N*-methyl isatins were used, **10** and **11** were obtained in both high yield and d.r. (Table 3, entries 6–9). The stereochemistry of **10** was established through single-crystal X-ray analysis of **10f** (Figure 2).^[13] Similar to the reaction with aldehydes, the reaction of diazo compound **1b** with the electron-withdrawing 5-nitro isatin gave **10h/11h** in high isolated yield

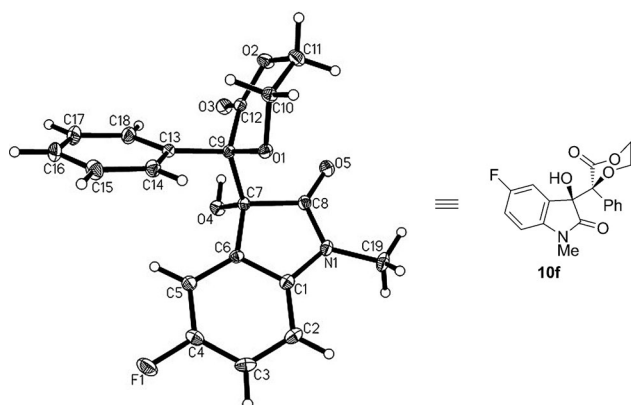


Figure 2. ORTEP illustration of **10f**.

(Table 3, entry 10), while no desired trapping product was obtained with the electron-donating diazo compound **1c** (Table 3, entry 11).

In conclusion, Cu(hfacac)₂-catalyzed trapping of intramolecularly formed protic oxonium ylides with electron-deficient aldehydes and isatins was successfully achieved. The reaction afforded oxygen-containing heterocyclic frameworks bearing the 3-substituted 1,4-dioxan-2-one moiety in moderate to good yield with high diastereoselectivity. This is the first example of an intramolecularly formed protic oxonium ylide trapping process. The success of the trapping reaction also provides experimental evidence for the existence of the protic oxonium ylide intermediate for rhodium- and copper-catalyzed intramolecular O–H insertion of diazo compounds.

Acknowledgements

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Keywords: aldol-type reaction • heterocycles • quaternary carbon • tandem reactions • ylides

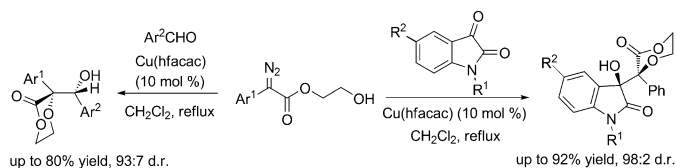
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Ylides

Xin Guo, Wei Liu,
Wenhao Hu*



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