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Enantioselective Trapping of Oxonium Ylides by 3-Hydroxyisoindolinones via a Formal S_N1 Pathway for Construction of Contiguous Quaternary Stereocenters

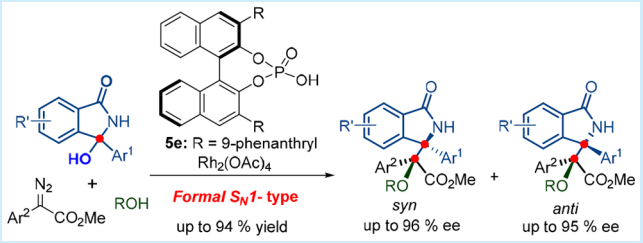
Zhenghui Kang,[†] Dan Zhang,[‡] Jiayi Shou,[†] and Wenhao Hu*[,†,‡]

[†]Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, School of Chemistry and Molecular Engineering, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, China

[‡]School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China

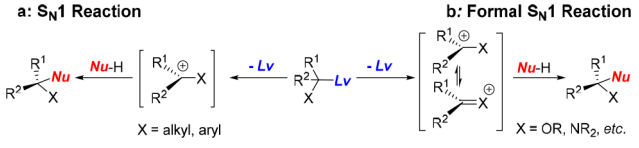
Supporting Information

ABSTRACT: An enantioselective Rh(II)/chiral phosphoric acid co-catalyzed three-component reaction via trapping of oxonium ylides with 3-hydroxyisoindolinones by a formal S_N1 pathway is described. This reaction allows for the efficient synthesis of isoindolinone derivatives with two contiguous quaternary stereogenic centers in high yields (up to 93%) with excellent enantioselectivities and moderate diastereoselectivities under mild reaction conditions.



Construction of chiral quaternary carbon stereocenters in an asymmetric catalytic manner remains one of the most challenging and demanding topics in modern organic chemistry.[1] Particularly, the intermolecular formation of C−C bonds between two contiguous quaternary stereogenic centers is extremely difficult due to the stronger steric hindrance and weaker C−C bond strength.[2] Thus, stereoselective control of contiguous quaternary centers is a problematic task owing to harsh conditions for the bond formation. Efforts have been devoted to addressing these challenges over the past few decades, mainly focusing on nucleophilic addition and radical reactions.[2,3] On the other hand, enantioselective S_N1-type nucleophilic substitution at the sp^3-hybridized carbon atom of racemic electrophiles is one of the most classical and powerful methods for the formation of covalent bonds (Scheme 1a).[4]

Scheme 1. Asymmetric Nucleophilic Substitution of Racemic Tertiary Electrophiles



However, enantioselective S_N1 reactions are far less developed than the nucleophilic addition reactions because of the difficult enantiocontrol of the active planar cationic intermediate generated as an electrophile in S_N1 reactions.[4a,b] Recent enhancements for the control of enantioselectivity in nucleophilic substitution between a racemic electrophile and a nucleophile in the formal S_N1 pathway involve introducing a heteroatom adjacent to the procarbocationic center so that the resultant cabocation can be stabilized by lone pair electrons on the heteroatom (Scheme 1b).[5,6] For example, introduction of a N/O atom can convert the carbonium ions into stabilized *N*-acyliminium/oxocarbenium ions.[5,6] Various nucleophiles, such as silyl ketene acetals,[5a] alcohols[5b] indoles,[5c] and so forth have been demonstrated via the formal S_N1 reaction. However, only one chiral quaternary stereocenter has been constructed. The enantioselective construction of contiguous quaternary stereocenters by the formal S_N1 pathway has not yet been reported.

Multicomponent reactions involving trapping of onium-ylides generated in situ from metal carbenoids have gained significant attention for the construction of complex molecules with high diversity and selectivity accompanied by high atom and step economy in recent years. Trapping of onium ylides with a wide scope of reactive electrophiles via nucleophilic addition to the prochiral sp^2-hybridized carbon atom of double bonds (e.g., C=O, C=N, and C=C) has been reported by us and other research groups (Scheme 2a).[7,8] In light of the unique nucleophilicity of the onium ylide intermediates,[9] we envisioned that the onium ylides could be employed in the enantioselective nucleophilic substitution at the sp^3-hybridized carbon atom of racemic 3-aryl-3-hydroxyisoindolinones by means of the formal S_N1 pathway via the in situ generated *N*-acyl ketiminium[6] in the presence of Brønsted acid (Scheme 2b). The reaction could give rise to two contiguous chiral quaternary stereocenters containing an isoindolin-1-one moiety.

The reaction of 3-phenyl 3-hydroxyisoindolinone (**3a**) with methyl phenyldiazoacetate (**1a**) and benzyl alcohol (**2a**) in the presence of both $[PdCl(\eta^3\text{-}C_3H_5)]_2$[10,7b,8c] and *rac*-phosphoric acid in dichloromethane at 25 °C was initially tested. Desired

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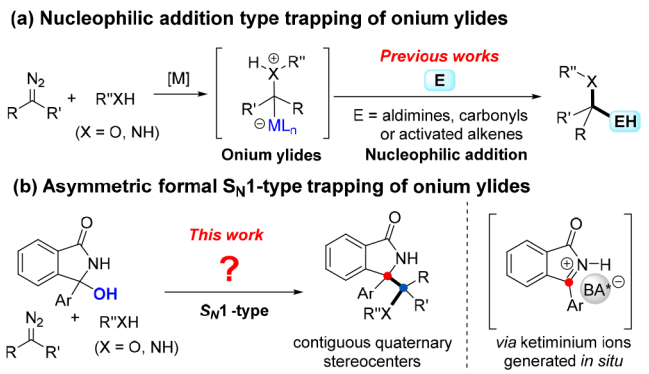
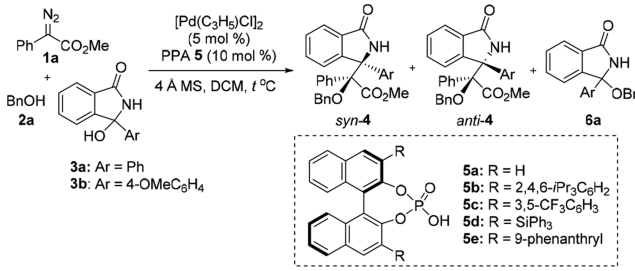
Scheme 2. Trapping Onium Ylides with 3-Hydroxyisoindolinone via the Formal S_N1 Pathway



product **4aa** was observed in moderate yield along with **6a** derived from the reaction of **3a** and **2a** as the main side product (Table 1, entry 1). The yield of **4aa** was enhanced to 90%, but

Table 1. Selected Optimization Studies[a]



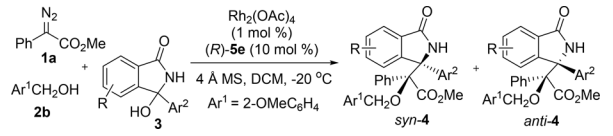
entry	3	PPA	t	yield[b] (%)	dr[c]	ee[d] (%)
1	**3a**	*rac*-**5a**	25	**4aa**: 50	71:29	
2	**3a**	*rac*-**5a**	40	**4aa**: 90	69:31	
3	**3a**	**5b**	40	**4aa**: 80	76:24	0/0
4	**3a**	**5c**	40	**4aa**: 85	56:44	0/0
5	**3a**	**5d**	40	**4aa**: 76	56:44	0/0
6	**3a**	**5e**	40	**4aa**: 90	58:42	26/21
7	**3a**	**5e**	0	trace		
8	**3b**	**5e**	0	**4ab′**: 40	55:45	70/76
9[e]	**3b**	**5e**	0	**4ab′**: 62	53:47	74/64
10[e]	**3b**	**5e**	−20	**4ab′**: 30	51:49	84/80
11[e,f]	**3b**	**5e**	−10	**4ab**: 70	57:43	89/90
12[e,f]	**3b**	**5e**	−20	**4ab**: 65	60:40	91/95

[a]Unless otherwise noted, all reactions were conducted on a 0.2 mmol scale of **3**, **1**:**2**:**3** = 1.5:1.2:1. [b]Combined yield of *anti*- and *syn*-isomers after isolation. [c]Ratio of *syn*/*anti* determined by crude ^{1}H NMR. [d]The ee for *syn*-**4**/ee for *anti*-**4** determined by HPLC analysis using a chiral stationary phase. [e]$Rh_2(OAc)_4$ (1 mol %) instead of $[PdCl(\eta^3\text{-}C_3H_5)]_2$. [f]2-Methoxybenzyl alcohol **2b** instead of benzyl alcohol **2a**.

the temperature has to be elevated to 40 °C (entry 2).[11] Different chiral BINOL-derived phosphoric acids (PPA) were then evaluated to fulfill catalytic enantioselective control (entries 3−6)[11] among which only **5e** was found to afford **4aa** in an enantioselective manner (entry 6) under such conditions. For improving the enantioselectivity, the temperature was reduced to 0 °C, but no desired product was obtained (entry 7) due to the low reactivity of **3a** at 0 °C. For increasing the reactivity of the substrate, the introduction of a *p*-methoxyphenyl substituent on the 3-aryl-3-hydroxyisoindolinone backbone (**3b**) resulted in product **4ab′** in 40% yield with substantially enhanced ee (70% ee for *syn*-isomers, 76% ee for *anti*-isomers) and moderate dr (entry 8). Further investigation of chiral PPA revealed that **5e** was the best Brønsted acid catalyst for the reaction.[11] When changing $[PdCl(\eta^3\text{-}C_3H_5)]_2$ to $Rh_2(OAc)_4$, a significant increase in yield was observed, but the ee and dr remained unaffected (entry 9). Further optimizations under $Rh_2(OAc)_4$ catalysis indicated that the enantioselectivity could be improved by lowering the temperature to −20 °C but at the expense of reaction yield (entry 10). After screening various benzyl alcohols and temperatures, significant improvement of yields and enantioselectivities were observed by replacing benzyl alcohol with 2-methoxybenzyl alcohol to afford **4ab** in the presence of $Rh_2(OAc)_4$ and **5e** at −20 °C (entries 11 and 12).[11]

Having established optimal conditions, we turned our attention to evaluating the substrate scope for this Rh(II)/chiral PPA-*co*catalyzed three-component reaction. A series of 3-aryl-3-hydroxyisoindolinones **3** were subjected to the desired transformation with **1a** and **2b**, and the reaction afforded the corresponding products **4** in good yields with high enantioselectivities and moderate diastereoselectivities (Table 2). Isoindolinones **3** bearing *p*-alkoxy substituents on Ar^2

Table 2. Substrate Scope of 3-Hydroxyisoindolinones[a]



entry	product	3	4: yield (%)[b]	dr[c]	ee (%)[d]
1		**3c**: Ar^2 = 4-$BnOC_6H_4$	**4ac**: 72	58:42	89/91
2		**3d**: Ar^2 = 4-$EtOC_6H_4$	**4ad**: 78	50:50	87/90
3		**3e**: Ar^2 = 4-$(NMe_2)C_6H_4$	**4ae**: 86	73:27	93/90
4[e]		**3f**: Ar^2 = 4-(N-morpholino)C_6H_4	**4af**: 92	64:36	95/93
5		**3g**: Ar^2 = 3-Me-4-$MeOC_6H_3$	**4ag**: 76	59:41	95/94
6		**3h**: Ar^2 = 3,4-$(MeO)_2C_6H_3$	**4ah**: 59	54:46	76/79
7		**3i**: R = Me, Ar^2 = 4-$MeOC_6H_4$	**4ai**: 82	50:50	80/92
8		**3j**: R = Cl, Ar^2 = 4-$MeOC_6H_4$	**4aj**: 86	48:52	80/91
9		**3k**: R = Me, Ar^2 = 4-(1-pyrrolidino)C_6H_4	**4ak**: 79	62:38	94/85
10[e]		**3l**: R =Me Ar^2 = 4-(N-morpholino)C_6H_4	**4al**: 94	67:33	96/92
11[e]		**3m**: R =Cl Ar^2 = 4-(N-morpholino)C_6H_4	**4am**: 90	57:43	90/92
12		**3n**: Ar^2 = 4-$MeOC_6H_4$	**4an**: 69	50:50	88/87
13[e]		**3o**: Ar^2 = 4-(N-morpholino)C_6H_4	**4ao**: 92	66:34	91/90

[a]Unless otherwise noted, all reactions were conducted on a 0.2 mmol scale of **3**, **1**:**2**:**3** = 1.5:1.2:1. [b]Combined yield of *anti*- and *syn*-isomers after isolation. [c]Ratio of *syn*/*anti* determined by crude ^{1}H NMR. [d]The ee for *syn*-**4**/ee for *anti*-**4** determined by HPLC analysis using a chiral stationary phase. [e]Performed at 25 °C.

proceeded efficiently to provide the corresponding products (**4ac**−**4ad**) in good yields and enantioselectivities with moderate diastereoselectivities. When more electron-rich 4-*N*,*N*-dialkylamino groups were placed on Ar^2, a significant increase in yields and enantioselectivities was observed, and products **4ae** and **4af** were furnished in excellent yields and enantioselectivities. Notably, the substrate with a 4-*N*-

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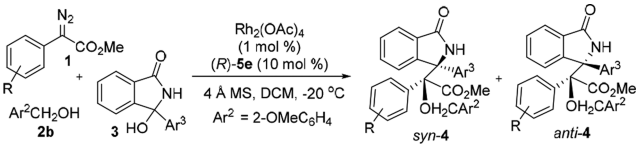
morpholino group on Ar^2 could afford product **4af** in 92% yield with excellent enantioselectivities (95% ee for *syn*-**4af** and 93% ee for the *anti*-**4af**) at 25 °C. These observations indicate the electron-donating property of the aryl groups at the C-3 position (Ar^2) plays a pivotal role in the trapping process. Similar results (**4ag**: 76% yield, *syn*/*anti* 59:41, 95%/94% ee) were obtained using the substrate with a 4-methoxy-3-methyl substituent on Ar^2. Isoindolinone motifs bearing different substituents were then surveyed. A 5,6-dimethyl or dichloro substituent on the phthalimide aromatic ring did not change the efficiency of the reaction and gave the products **4ai**–**4am** in good yields with high enantioselectivities. Moreover, the substrates with a naphthalene ring were also effective for providing **4an** or **4ao** in good yields and high ee values.

To further elaborate the substrate scope, we then investigated a variety of diazo compounds with **2b** and **3**. As shown in Table 3, in the case of Ar^3 = 4-$MeOC_6H_4$, methyl

Table 3. Substrate Scope of Diazo Compounds[a]



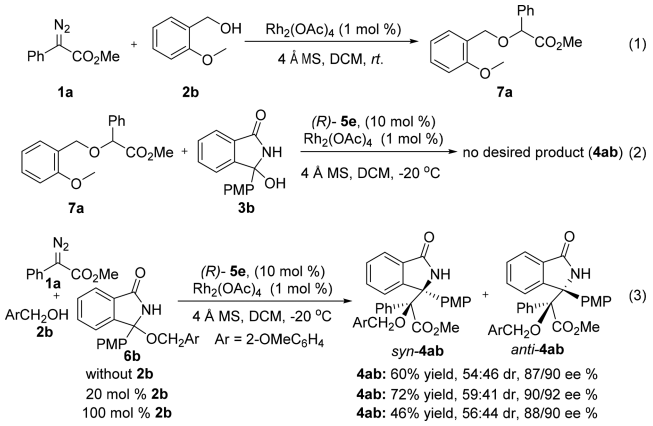
entry	3	1:R	4: yield (%)[b]	dr[c]	ee[d] (%)
1	**3b**	**1b**: 4-Cl	**4bb**: 70	54:46	89/93
2	**3b**	**1c**: 4-Br	**4bc**: 78	45:55	87/91
3	**3b**	**1d**: 4-Me	**4bd**: 75	46:54	90/94
4	**3b**	**1e**: 4-OMe	**4be**: 82	47:53	85/91
5	**3b**	**1f**: 3-Br	**4bf**: 72	57:43	85/93
6	**3b**	**1g**: 3-OMe	**4bg**: 81	51:49	94/95
7	**3b**	**1h**: 3,4-diMe	**4bh**: 83	39:61	90/94
8[e]	**3f**	**1i**: 4-F	**4fi**: 90	66:34	95/92
9[e]	**3f**	**1c**: 4-Br	**4fc**: 90	64:36	91/90
10[e]	**3f**	**1e**: 4-OMe	**4fe**: 93	62:38	94/92
11[e]	**3f**	**1g**: 3-OMe	**4fg**: 92	65:35	93/91
12[e]	**3f**	**1h**: 3,4-diMe	**4fh**: 93	60:40	95/93

[a]Unless otherwise noted, all reactions were conducted on a 0.2 mmol scale of **3**, **1**:**2**:**3** = 1.5:1.2:1. [b]Combined yield of *anti*- and *syn*-isomers after isolation. [c]Ratio of *syn*/*anti* determined by crude ^{1}H NMR. [d]The ee for *syn*-**4**/ee for *anti*-**4** determined by HPLC analysis using a chiral stationary phase. [e]Performed at 25 °C.

aryldiazo acetates bearing either electron-withdrawing or -donating substituents at the ortho, meta, or para positions of the phenyl ring were found to react successfully with **2b** and **3b**, leading to the desired products **4bb**–**4bh** in good yields (70–83%) with high ee (up to 95%). The highest ee value (94% ee for *syn*-**4bg**, 95% ee for *anti*-**4bg**) was obtained in the case of Ar^1 = 3-$MeOC_6H_4$. Importantly, when Ar^3 = 4-*N*-morpholino phenyl, the reaction maintained its high efficiency at 25 °C, affording **4fi**–**4fh** in significantly increased yields (90–93%) with excellent enantioselectivities (90–95% ee) regardless of the position and electronic nature of the substituents on the phenyl ring of the diazo compounds (entries 8–12).

Control experiments starting from the O–H insertion product **7a** and **3b** were conducted under the standard conditions in which no three-component product was observed. The result excludes the possibility that desired product **4** was formed through a stepwise O–H insertion/Mannich addition pathway (Scheme 3, eqs 1 and 2). Furthermore, no desired product was obtained, and the corresponding O–H insertion

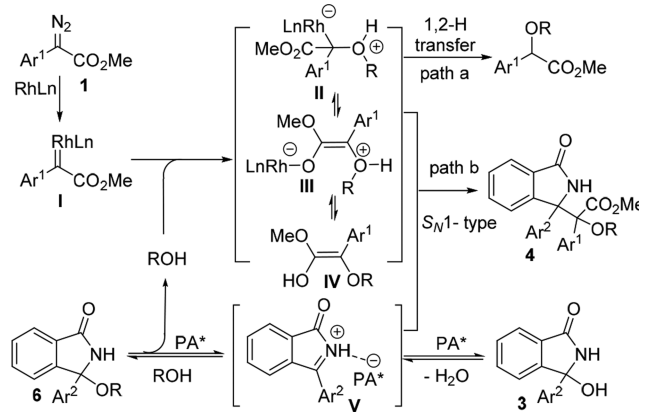
Scheme 3. Control Experiments



product was observed when the model reaction was performed without chiral PPA, or *N*-methylated 3-hydroxyisoindolinone was employed as substrate under the otherwise identical reaction conditions.[12] These experiments indicate the requirement of a free N–H functionality and the essential role of chiral PPA for the successful formation and activation of a ketiminium intermediate.[13] Additional control experiments (Scheme 3, eq 3) demonstrated that **6b**, with or without **2b**, could convert to product **4ab** under the reaction conditions. These observations strongly support that there is chemical equilibrium between **6b** and the ketiminium intermediate (**V**).[14]

On the basis of the mechanistic investigations described above, we posit a possible mechanism as shown in Scheme 4.

Scheme 4. Proposed Mechanism



N-Acyl ketiminium ions (**V**) formed from the dehydration of **3** establish chemical equilibrium with **6** and **2** rapidly in the presence of chiral PPA.[14] Meanwhile, $Rh_2(OAc)_4$ decomposes diazo compounds **1** to form electrophilic rhodium carbene intermediate **I**, which reacts with alcohol **2** to give rhodium-associated oxonium ylide intermediate **II** and its enolate counterpart **III**. In addition, intramolecular proton transfer may give corresponding enol form **IV**.[15] The resulting intermediates **II**, **III**, or **IV** react with the *N*-acyl ketiminium (**V**) immediately to provide products **4**.

In conclusion, we have developed a $Rh_2(OAc)_4$ and chiral PPA-cocatalyzed enantioselective formal S_N1 reaction between a racemic 3-hydroxyisoindolinone and a transient oxonium ylide by means of the Mannich-type pathway. This approach is an unprecedentedly catalytic enantioselective S_N1-type process

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for the onium ylide trapping via ketiminium generated in situ. This method provides facile access to the construction of two contiguous quaternary carbon centers, and a range of optically active multisubstituted isoindolinone derivatives can be obtained from simple starting materials with good yields and high enantioselectivities. Efforts are ongoing to improve the diastereoselectivities and understand the mechanism better.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03916.

Experimental procedures and characterization for new compounds including NMR spectra (PDF)

Accession Codes

CCDC 1583165 and 1587746 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: huwh9@mail.sysu.edu.cn.

ORCID

Dan Zhang: 0000-0003-0200-8527

Wenhao Hu: 0000-0002-1461-3671

Notes

The authors declare no competing financial interest.

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