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Iridium-Catalyzed Selective Synthesis of 4-Substituted Benzofurans and Indoles *via* Directed Cyclodehydration

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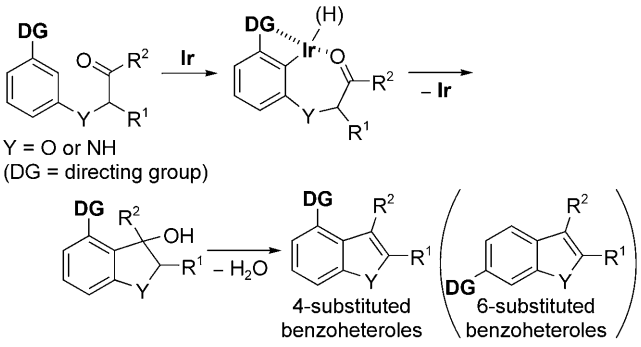
Abstract: A directed cyclization-dehydration cascade of α-aryloxy ketones and α-arylamino ketones was efficiently catalyzed by a cationic iridium-BINAP complex, which afforded various types of 4-substituted benzofurans and indoles in high yields with complete regioselectivity. The newly developed protocol also enabled the enantioselective preparation of chiral 4-acetyloxindole using a chiral iridium catalyst.

Keywords: C–C bond formation; C–H functionalization; heterocycles; homogeneous catalysis; iridium

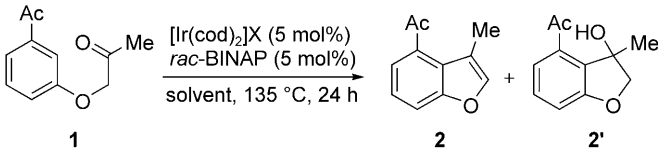
Heterocycles are a ubiquitous class of compounds in nature. Benzofuran and indole scaffolds are particularly of great interest and are widespread in a myriad of bioactive compounds and pharmaceutical agents.[1] Therefore, many organic chemists have been prompted to develop various efficient synthetic protocols for the preparation of these target compounds.[2,3] Among these protocols, cyclodehydration, namely the cyclization-dehydration cascade of α-aryloxy ketones and α-arylamino ketones is an attractive and reliable strategy because (i) the starting materials can be readily prepared, (ii) the C–H bond can be directly functionalized in the cyclization process, and (iii) the waste by-product is water.[4] However, substitution on the arene moiety often invokes the issue of regioselectivity. The application to the synthesis of 4-substituted benzoheteroles is especially challenging, because the *meta*-substituted precursors tend to cyclize at the less hindered *ortho* position, leading to the predominant formation of 6-substituted benzoheteroles or a mixture of 6-substituted and 4-substituted benzoheteroles.[5,6] Moreover, excess or stoichiometric amounts of strong Brønsted acids or Lewis acids are required in most cases.[7] Consequently, the development of versatile alternatives using a mild catalyst for the selective synthesis of 4-substituted benzoheteroles is highly desired. We herein report the successful realization of this challenging transformation by cationic iridium-catalyzed cyclodehydration using a directing group. From the results obtained in this report, we assumed that the installation of a directing group at the *meta* position enabled carbon-iridium bond formation at the congested *ortho* position through C–H bond cleavage or an electrophilic metallation mechanism.[8,9] Subsequently, intramolecular 1,2-addition to a carbonyl moiety[10] and dehydration yielded 4-substituted benzoheteroles as the sole regioisomer (Scheme 1).[11]

Our group has disclosed that cationic rhodium- and iridium-biaryl diphosphine complexes can operate as effective catalysts in the directed sp^2 C–H bond activation of aryl ketones.[12] Very recently, we also realized sp^3 C–H bond activation of amides by cationic iridium catalysis.[13] Therefore, these cationic metal species were tested in the cyclization of 1-(3-acetylphe-



Scheme 1. A proposed mechanism for the iridium-catalyzed directed cyclization-dehydration cascade of α-aryloxy ketones and α-arylamino ketones.

Table 1. Optimization of the reaction conditions.[a]



1 2 2'

Entry	X[b]	Yield of **2** [%][c]	Yield of **2′** [%][c,d]
1[e]	OTf	6	6
2	OTf	71	n.d.
3	BF_4	48	4
4	SbF_6	85	n.d.
5	BARF	94	n.d.
6[f]	BARF	94	n.d.

[a] Unless otherwise noted, *reaction conditions* were as follows: substrate **1** (0.1 mmol), $[Ir(cod)_2]X$ (5 μmol), *rac*-BINAP (5 μmol), PhCl (0.2 mL), 135 °C, 24 h.

[b] OTf = trifluoromethanesulfonate, BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

[c] Isolated yield.

[d] n.d. = not detected.

[e] Performed in 1,2-dichloroethane at 95 °C.

[f] Substrate **1** (0.25 mmol), $[Ir(cod)_2]$BARF (2.5 μmol), *rac*-BINAP (2.5 μmol), PhCl (0.1 mL), 160 °C under microwave irradiation (200 W), 20 min.

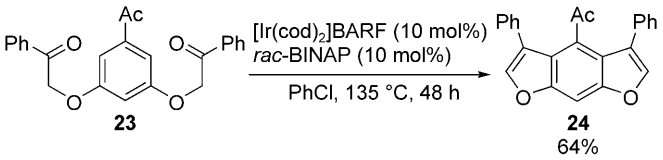
noxy)propan-2-one (**1**). Initial screening revealed that the cationic iridium-BINAP complex afforded 4-acetylbenzofuran **2** and benzofuranol **2′** in low yield at 95 °C (Table 1, entry 1), whereas the corresponding rhodium catalyst did not afford any cyclized products. A higher temperature (135 °C) improved the conversion of aryloxy ketone **1** along with the complete dehydration of benzofuranol **2′** (Table 1, entry 2). Further optimization of the reaction conditions also revealed that the counteranion of the iridium complex significantly affected the product yield (Table 1, entries 3–5): the tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate anion (BARF) was found to be optimal and benzofuran **2** was obtained in excellent yield without the formation of undesired 6-substituted benzofuran (Table 1, entry 5). Moreover, short-time synthesis was achieved under microwave irradiation, using only 1 mol% of the catalyst (Table 1, entry 6). Although the Ir^+/PPh_3 system afforded the product in acceptable yield (77% NMR yield), ligands other than BINAP and PPh_3 were ineffective (see Table S1 in the Supporting Information).

To shed light on the reaction mechanism, 1-phenoxypropan-2-one, an electron-rich and directing group-free variant, was subjected to cyclization under the same reaction conditions as entry 5 in Table 1; however, in this reaction, the corresponding benzofuran was not obtained at all. This result suggests that the present iridium-catalyzed cyclodehydration should proceed *via* directed C–H bond cleavage or electrophilic metallation, as depicted in Scheme 1, rather than a Friedel–Crafts-type reaction.[14]

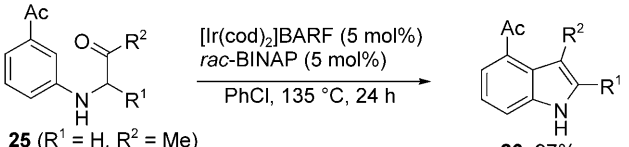
The directed cyclodehydration of several types of α-aryloxy ketones was then examined under the established iridium-based catalytic system (Table 2 and Scheme 2). In all runs, efficient syntheses of 4-substituted benzofurans were achieved, along with complete regioselectivity. Cyclization of α-aryloxy *tert*-butyl ketone **3** and α-aryloxy phenyl ketone **5** successfully proceeded to afford the 4-acetylbenzofurans, possessing a bulky substituent at the C-3 position, in excellent yield (Table 2, entries 1 and 2). Substitution at the α-position of the carbonyl moiety was tolerated: 2,3-dimethylbenzofuran **8**, tricyclic benzofuran **10**, and 2-anisylbenzofuran **12** were obtained in high yields (Table 2, entries 3–5).

Subsequently, the effect of the substituent at the arene moiety was investigated. It was found that a methoxy group could be installed on any position, and the corresponding 4-acetylbenzofurans were efficiently obtained as sole regioisomers (Table 2, entries 6–8). Notably, in addition to the acetyl group, ester and amide moieties also operated as effective directing groups, leading to the selective formation of 4-methoxycarbonylbenzofuran **20** and 4-acetylaminobenzofuran **22** (Table 2, entries 9 and 10).[15] Moreover, the iridium catalyst promoted the double cyclodehydration of 5-acetylresorcinol ether **23** to provide 4-acetylbenzodifuran **24** (Scheme 2).[16]

The current iridium catalysis was also applicable to the directed cyclodehydration of α-arylaminoketones (Scheme 3). As was the case for benzofuran synthesis, several types of 4-acetylindoles were selectively obtained in satisfactory yield. It is noteworthy that the substrates possessing an amine moiety could be directly subjected to the reaction to yield protection-



Scheme 2. Synthesis of benzodifuran **24** *via* the iridium-catalyzed double cyclodehydration.

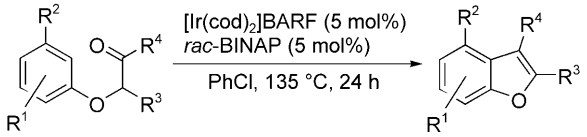


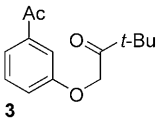
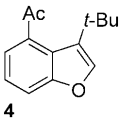
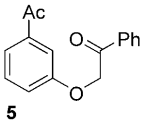
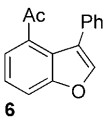
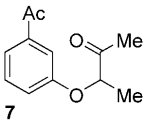
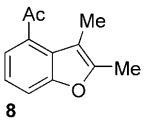
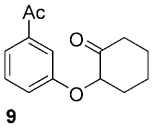
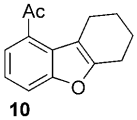
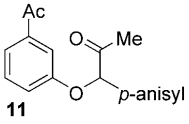
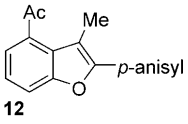
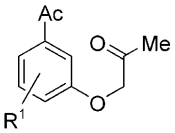
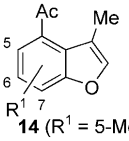
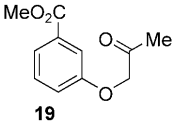
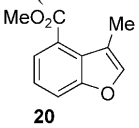
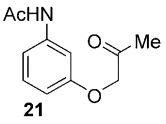
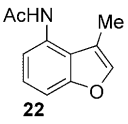
25 (R^1 = H, R^2 = Me)
27 (R^1 = H, R^2 = Ph)
29 (R^1 = Me, R^2 = Me)
31 [R^1, R^2 = -$(CH_2)_4$-]

26: 97%
28: 83%
30: 85%
32: 72%

Scheme 3. Synthesis of unprotected 4-acetylindoles.

Table 2. Synthesis of 4-substituted benzofurans.[a]



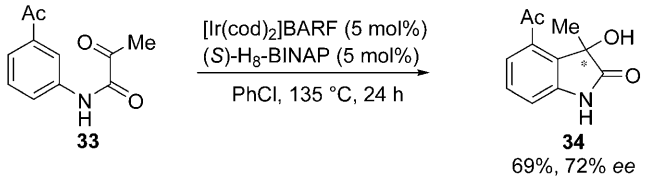
Entry	Substrate	Product	Yield [%][b]
1	 **3**	 **4**	95
2	 **5**	 **6**	94
3	 **7**	 **8**	88
4	 **9**	 **10**	84
5	 **11**	 **12**	87
6	 **13**	 **14** (R^1 = 5-MeO)	87
7	**15**	**16** (R^1 = 6-MeO)	quant.
8	**17**	**18** (R^1 = 7-MeO)	95
9	 **19**	 **20**	82
10	 **21**	 **22**	84

[a] *Reaction conditions:* substrate (0.1 mmol), [Ir(cod)$_2$]BARF (5 μmol), *rac*-BINAP (5 μmol), PhCl (0.2 mL), 135 °C, 24 h.
[b] Isolated yield.

free 4-acetylindoles, which is an apparently difficult transformation in the case of strong acid catalysts.

Finally, the iridium-catalyzed cyclization of pyruvamide derivative **33** was examined (Scheme 4). Intriguingly, dehydration did not proceed and the *tert*-alcohol moiety remained intact, resulting in the selective formation of chiral 4-acetyloxindole **34**. To extend this reaction to an enantioselective variant, several chiral ligands were then examined. It was found that the use of (*S*)-H$_8$-BINAP was effective and the product was afforded with acceptable enantioselectivity.

In conclusion, we have discovered the high catalytic activity of a cationic iridium-BINAP complex in the directed cyclodehydration of α-aryloxy ketones. Various types of substrates efficiently participated in the transformation, affording the corresponding 4-substituted benzofurans with complete regioselectivity.



Scheme 4. Enantioselective synthesis of 4-acetyloxindole **34**.

Along with the acetyl group, ester and amide moieties also functioned as directing groups. Moreover, the established protocol was successfully applied to the synthesis of protection-free 4-acetylindoles and the enantioselective synthesis of chiral 4-acetyloxindole. Further modification of the catalytic system, elucidation of the detailed reaction mechanism, and application to natural product synthesis are in progress.

Experimental Section

Typical Experimental Procedure (Table 1, entry 5)

$[Ir(cod)_2]$BARF (6.7 mg, 5 μmol) and *rac*-BINAP (3.2 mg, 5 μmol) were placed in an oven-dried Schlenk tube, which was then evacuated and backfilled with argon (×3). 1-(3-Acetylphenoxy)propan-2-one (**1**, 19.3 mg, 0.1 mmol) and PhCl (0.2 mL, pre-treated by argon bubbling) were added to the reaction vessel. The solution was then stirred at 135 °C for 24 h. The resultant mixture was cooled to room temperature and the solvent was evaporated. The crude products were purified by thin-layer chromatography (hexane/ethyl acetate = 3:1) to yield analytically pure benzofuran **2**; yield: 16.6 mg (94%).

Acknowledgements

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