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Very Important Publication

Diastereoselective Intramolecular Aldol-Type Trapping of Zwitterionic Intermediates by Ketones for the Synthesis of Spiro[chroman-4,3′-oxindole] Derivatives

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Abstract: A simple, mild and efficient rhodium-catalyzed aromatic C–H functionalization of α-phenoxy ketones by 3-diazooxindoles for the synthesis of the spiro[chroman-4,3′-oxindole] ring system is described. A series of functionalized spiro[chroman-4,3′-oxindole] derivatives bearing two adjacent quaternary carbon centers have been attained in a highly diastereoselective manner with very good yields. Control experiments suggested the possibility of an intramolecular aldol-type trapping of zwitterionic intermediates after the C–H functionalization. Furthermore, the applicability of this method has been tested by a gram-scale synthesis. A facile treatment with base enabled the access to both *syn*- and *anti*-diastereomers *via* isomerization.

Keywords: aromatic C–H functionalization; rhodium; spiro[chroman-4,3′-oxindole] derivatives; trapping; zwitterionic intermediates

Heterocyclic spirooxindoles architectures have drawn the attention of many medicinal chemists in organic synthesis due to their existence as privileged scaffolds of important pharmacophores in pharmaceuticals and also as the core structure of alkaloid natural products.[1] Among them the oxindole structure with a tetrahydropyran ring junction at the C-3 position (Figure 1a) is one of the synthetic targets.[2] Recently, some efficient strategies have been successfully developed towards the synthesis of these spirooxindole analogues including [Pd]-catalyzed carbosilylation followed by cyclization of *N*-[2-(1,3-carbamoylbutenyl)aryl] chlorides,[3] formal [5+1] annulation of oxindoles and ester-linked bisenones,[4] the Prins cascade reaction of 4-hydroxy-*N*-methyl-2-methylene-*N*-phenylbutanamide and aldehydes,[5] and multi-component reactions (MCRs).[6] Nevertheless, a thorough literature survey indicated that there were limited developments in order to access the fused chroman-3-ol moiety at the C-3 position, although chroman-3-ol is also an important skeleton in natural/unnatural compounds of biological interest (Figure 1b).[7] It is worth mentioning that the two adjacent quaternary stereocenters present in the oxindole fused chroman-3-ol moiety at the C-3 position make this moiety difficult to construct. A few methods comprising a tandem Friedel–Crafts-type reaction of 2-naphthol[8a] or cas-

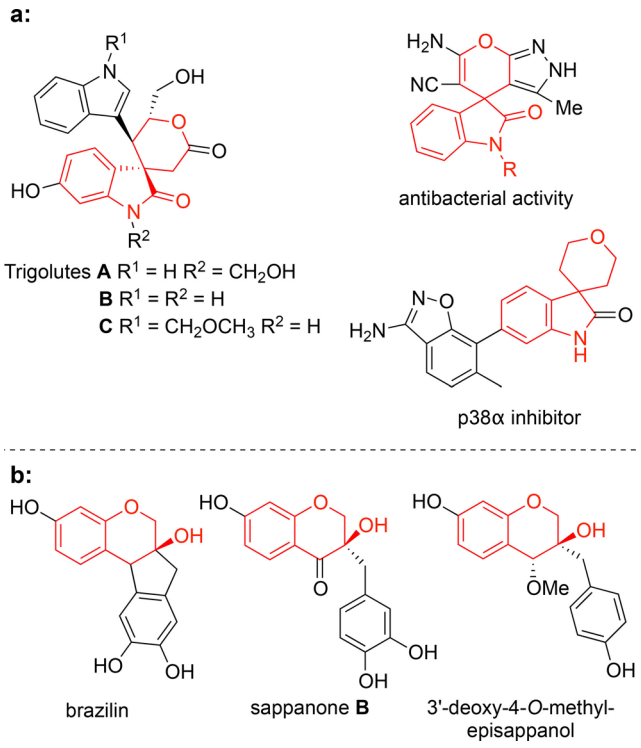
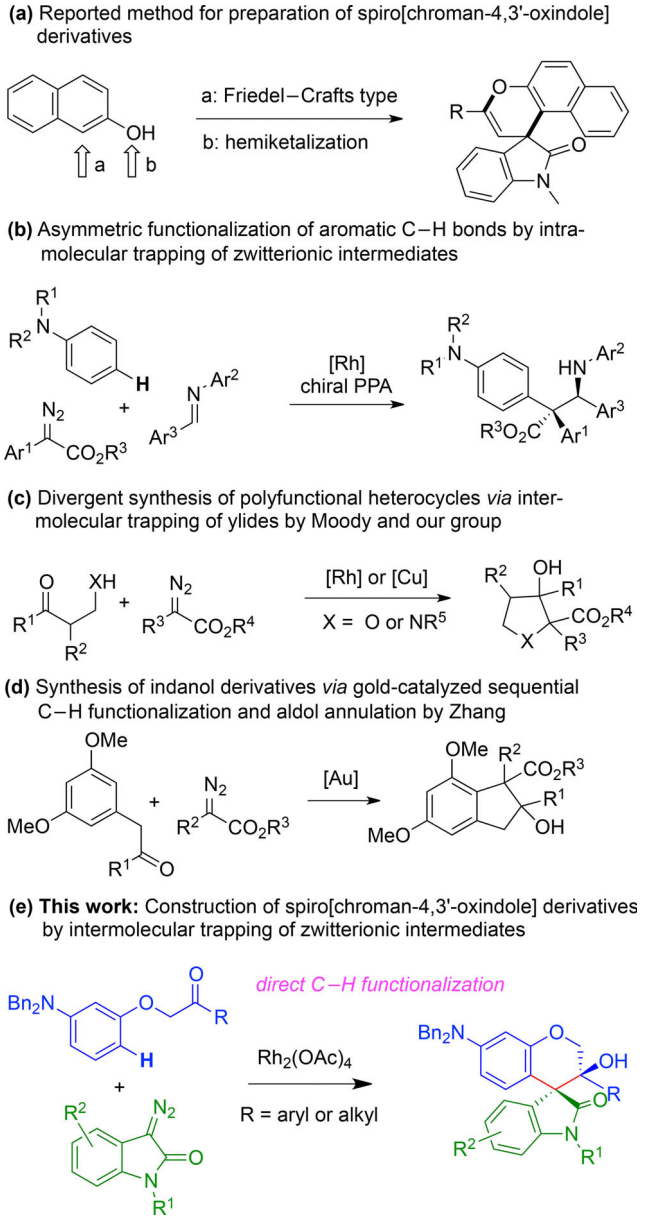


Figure 1. Spiro[tetrahydropyran-4,3′-oxindole] and chroman-3-ol skeletons in natural products and drugs.

cade Michael-addition of 8-hydroxyquinoline[8b] have been targeted to accomplish the key chroman ring in spiro[chroman-4,3′-oxindole] (Scheme 1a). However, the development of a straightforward and sensible method to access such skeletons from simple starting materials is highly desirable for drug development.

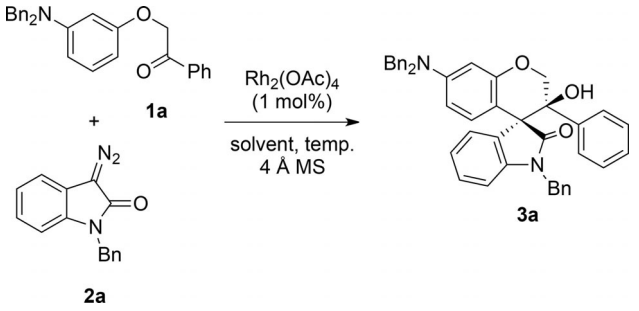
In this context multi-component reactions have become powerful tools in recent years to achieve complex molecules from corresponding simple units. Our research group has developed some important multi-component reactions through a metal carbene-induced active intermediate trapping process in which oxonium ylides[9] (generated from water or alcohols) or ammonium ylides[10] (generated from amines) as well as zwitterionic intermediates[11] (generated from indoles, pyrroles, *N*-substituted anilines etc.,) could be trapped by electrophiles such as aldehydes, ketones, imines, or α,β-unsaturated carbonyl compounds. Among them, we have achieved the asymmetric functionalization of aromatic C–H bonds through a three-component reaction of *N*,*N*-disubstituted anilines with diazo compounds and imines in the presence of Rh(II)/chiral phosphoric acid cocatalysts (Scheme 1b).[12] Recently, Moody[13] and our group[14] reported an intramolecular aldol-type trapping of oxonium/ammonium ylides for the synthesis of tetrahydrofurans/pyrrolidines from diazo compounds and β-hydroxy ketones/β-amino ketones (Scheme 1c). Similarly a gold-catalyzed sequential C–H functionalization and aldol annulation strategy was developed by Zhang[15] for the synthesis of indanol derivatives. However, in application to this method, only one example of a spirooxindole has been obtained, albeit possessing low diastereoselectivity (Scheme 1d). With our ongoing interest in the construction of polyfunctional heterocycles on the basis of these trapping tactics and aromatic C–H functionalizations, herein we have designed an intramolecular aldol-type trapping (not a sequential) of metal carbene-induced zwitterionic intermediates which could be generated *in-situ* from 3-diazooxindole and α-phenoxy ketones, to establish the spirooxindole fused chroman-3-ol moiety (Scheme 1e). This strategy shows the dual role of α-phenoxy ketones as both zwitterionic intermediate precursor and also as the intramolecular trapping reagent. It has been observed that the results with *N*,*N*-dibenzylaniline are better than those with other *N*-substituted aniline substrates in an intermolecular zwitterionic intermediate trapping process.[12] Hence, we decided to introduce dibenzylamino substitution on the phenyl ring of the α-phenoxy ketone to enrich the electronic density of the aromatic C–H bond.



Scheme 1. Strategies for the synthesis of spiro[chroman-4,3′-oxindole] derivatives.

Thus the synthetic strategy was initiated with the reaction of 2-[3-(dibenzylamino)phenoxy]-1-phenylethanone **1a** and 1-benzyl-3-diazoindolin-2-one **2a** in the presence of $[Rh_2(OAc)_4]$ catalyst and 4 Å molecular sieves at 0 °C in dichloromethane. To our delight, the desired product **3a** was obtained in 52% yield and with 90:10 diastereoselectivity (Table 1, entry 1). Both the yield and diastereoselectivity of **3a** were improved with an increase in temperature, but further increases in temperature reduced the yield (Table 1, entries 2 and 3). Various solvents were also screened in order to further improve the yield of **3a**. The reactions in toluene, xylene and $CHCl_3$ showed decrements in the yield of **3a** (Table 1, entries 4, 5 and 7). However, the desired product **3a** was obtained in 90% yield and 95:5 diastereoselectivity when the reaction was performed in 1, 2-dichloroethane (DCE) at 25 °C in the presence of 4 Å molecular sieves (Table 1, entry 6).

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



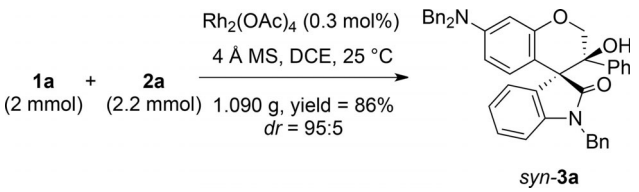
Entry	Solvent	Temp. [°C]	Yield [%][b]	*dr* (*syn*:*anti*)[c]
1	DCM	0	52	90:10
2	DCM	25	89	94:6
3	DCM	40	81	94:6
4	$PhCH_3$	25	77	94:6
5	Xylene	25	57	93:7
6	DCE	25	90	95:5
7	$CHCl_3$	25	66	83:17

[a] Reactions were conducted by adding **2a** (0.11 mmol) in 1 mL of the solvent to the mixture of **1a** (0.1 mmol) and catalyst in 1 mL of the solvent via syringe pump over 1 h.
[b] Isolated yield after column chromatography.
[c] Determined by ^{1}H NMR of crude mixture.

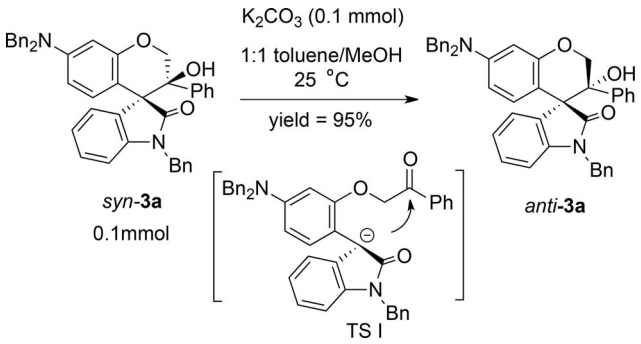
With the optimized reaction conditions in hand, the substrate scope of this transformation for the synthesis of spiro[chroman-4,3′-oxindole] derivatives **3** was examined. The current strategy showed very good substrate scope tolerating different aryl (from electron-donating to electron-withdrawing and heterocyclic) substituted α-phenoxyarylethanones **1** and resulted in the desired products **3** in very good yields with excellent diastereoselectivities. For example, excellent yield and diastereoselectivity were obtained in the case of electron-donating substituents on the aryl rings (Table 2, **3b**, **3c**, **3d**). A heterocyclic substituted substrate gave the corresponding product **3e** in 92% yield along with >95:5 diastereoselectivity. Naphthyl-substituted substrates also resulted in good yields (Scheme 2, **3f**). Meanwhile, the 2,4-dichlorophenyl substrate was also tolerated well, affording 79% yield and >95:5 diastereoselectivity (Table 2, **3g**). Notably, 4-CF_3-phenyl-substitution gave 72% yield and 24:76 diastereoselectivity (Table 2, **3h**). For this substrate, *anti*-**3h** was the major product, which perhaps was the result of partial isomerization of *syn*-**3h** under the standard reaction conditions. Crucially, methyl- and ethyl-substitution were also compatible with the standard conditions (Table 2, **3i**, **3j**). The more bulky butyl-substitution afforded the corresponding spiro-[chroman-4,3′-oxindole] in good yield with relatively low diastereoselectivity (Table 2, **3k**). In addition to other spectroscopic studies, the relative configuration of the desired product was unambiguously determined by X-ray analysis of **3b**.[16]

Furthermore, the scope with respect to the 3-diazooxindoles **2** was further investigated. Substituents on the C-5 and C-6 positions of 3-diazooxindoles **2** gave the desired products **3l–q** in good yields with high diastereoselectivities (Table 3, entries 1–6). Replacing the *N*-benzyl substituent of 3-diazooxindole by *N*-Cbz and *N*-Me slightly reduced the yield and diastereoselectivity (**3r** *vs.* **3a**, **3s** *vs.* **3a**, **3t** *vs.* **3l**).

To gain some insight into the reaction pathway of this intramolecular aldol-type trapping process, a control experiment was conducted to verify whether the current reaction proceeds *via* a stepwise or a concerted reaction pathway.[17] Thus the C–H insertion product **4a** was isolated and then treated under the identical reaction conditions of the current reaction, but no **3a** was observed. In this manner the control experiment excluded the possibility of a stepwise C–H insertion/aldol-type addition pathway. To demonstrate the synthetic efficiency of this process, a gram-scale reaction was carried out by using 2 mmol of **1a** and 2.2 mmol **2a**. To our delight the reaction proceeded smoothly under standard conditions to give the desired product **3a** in 86% yield (1.09 g) with 95:5 diastereoselectivity (Scheme 2). Interestingly, on treatment with an equivalent of K_2CO_3 in toluene and MeOH at room temperature, *syn*-**3a** isomerized to its diastereomer *anti*-**3a** totally in 95% yield. The isomerization of *syn*-**3a** might be possibly due to an intramolecular retro-aldol reaction *via* transition state **I** to give the thermodynamically stable *anti*-**3a** (Scheme 3). On the other hand, similar K_2CO_3 treatment on insertion product **4a** did not result *anti*-**3a,** which revealed that the *anti*-**3a** was not produced from the insertion

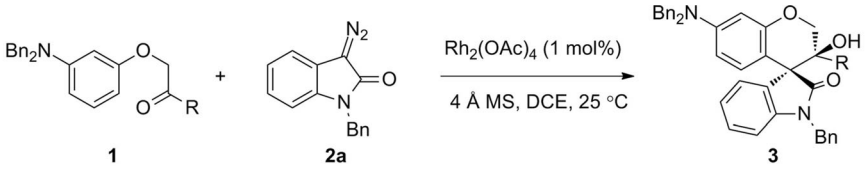


Scheme 2. Gram-scale reaction.



Scheme 3. Diastereomer switching experiment.

Table 2. Scope of the α-phenoxy ketones.[a],[b],[c]



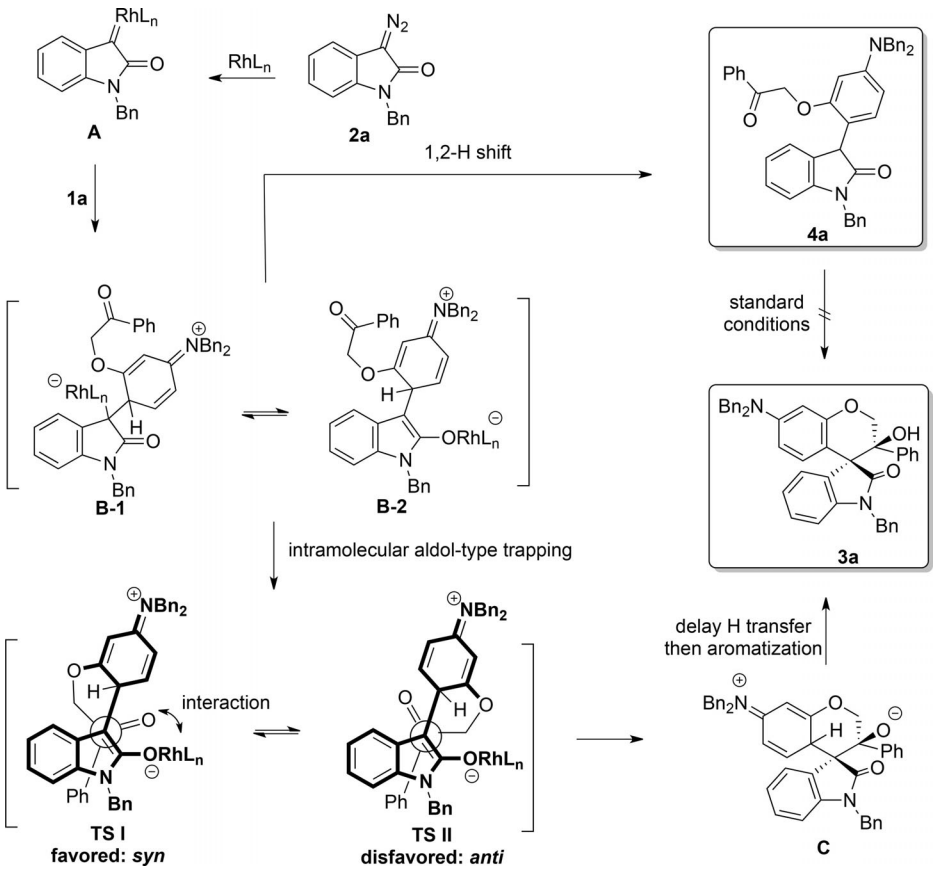
[a] Reactions were conducted by adding **2a** (0.11 mmol) in 1 mL of the solvent to the mixture of **1a** (0.1 mmol) and catalyst in 1 mL of the solvent via syringe pump over 1 h.
[b] Isolated yield after column chromatography.
[c] Determined by ^{1}H NMR of crude mixture.[a] Unless otherwise noted, all reactions were conducted by adding **2a** (0.33 mmol) and **1** (0.3 mmol) under standard conditions *via* syringe pump over 1 h, and the reaction mixture was stirred for another 10 min.
[b] Isolated yield after column chromatography.
[c] The *dr* was determined by ^{1}H NMR of the crude mixture.

product **4a**.[17] Furthermore, this *syn* to *anti* isomerization broadens the scope of the current strategy as we could accomplish both the diastereomers conveniently in a highly diastereoselctive manner.

A plausible reaction pathway is proposed in Scheme 4 based on the control experiments. Firstly, 3-diazooxindole **2a** formed metal carbene **A** in the presence of $Rh_2(OAc)_4$. Then active metal carbene-induced zwitterionic intermediate **B-1**[18] or its enolate form **B-2** was generated by the interaction between **1a** and metal carbene **A**. A traditional 1,2-H shift gave the C–H insertion product **4a**, while a novel intramolecular electrophilic trapping went ahead to afford the intermediate **C**. Finally, the desired product **3a** was obtained by a delayed H-transfer and aromatization of the aromatic ring.

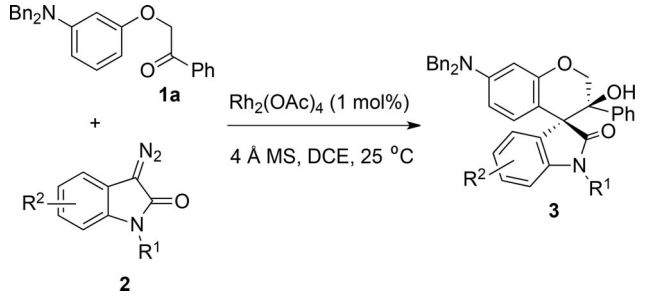
The observed stereoselective control of the reaction could be explained by comparing the transition states **I** and **II**. The interaction between the rhodium species and the carbonyl of **1a** facilitated the favored TS **I** compared to TS **II** which was disfavored.

In summary, we have developed an efficient method for the construction of spiro[chroman-4,3′-oxindole] derivatives in very good yields with excellent diastereoselectivities through aromatic C–H functionalization. Notably, α-phenoxyalkyl ketone substrates also underwent the reaction effectively and resulted in corresponding spiro systems in very good yields. This transformation offers a straightforward way for the construction of both the diastereomers of the spiro[chroman-4,3′-oxindole] skeleton and also enriches our trapping strategy in the functionalization of aro-



Scheme 4. Plausible reaction mechanism.

Table 3. Scope of 3-diazooxindoles[a]



Entry	3	R^1	R^2	Yield [%][b]	*dr* (*syn*:*anti*)[c]
1	**3l**	Bn	5-Me	87	95:5
2	**3m**	Bn	5-F	83	>95:5
3	**3n**	Bn	5-Cl	93	>95:5
4	**3o**	Bn	5-Br	86	94:6
5	**3p**	Bn	6-Cl	88	>95:5
6	**3q**	Bn	6-Br	85	93:7
7	**3r**	Cbz	H	76	93:7
8	**3s**	Me	H	82	94:6
9	**3t**	Me	5-Br	79	91:9

[a] Reactions were conducted by adding **2** (0.33 mmol) in 1 mL of the solvent to the mixture of **1a** (0.3 mmol) and catalyst in 1 mL of the solvent *via* syringe pump over 1 h.
[b] Isolated yield after column chromatography.
[c] Determined by ^{1}H NMR of crude mixture.

matic C–H bonds. The asymmetric version based on a Brønsted acid catalyst to activate the carbonyl group is currently investigated in our laboratory.

Experimental Section

Typical Procedure for Intramolecular Aldol-Type Trapping of Zwitterionic Intermediates

A mixture of $Rh_2(OAc)_4$ (0.003 mmol), **1** (0.3 mmol),and 4 Å MS (100 mg) in 1 mL of DCE under an argon atmosphere was stirred at room temperature. Diazo compound **2** (0.33 mmol) in 1 mL or 2 mL of DCE was then added over 1 h *via* a syringe pump. After completion of the addition, the reaction mixture was stirred for another 0.5 h, then filtered and evaporated under vacuum to give the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc/light petroleum ether = 1:10–1:5) to give the pure product.

Acknowledgements

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[16] CCDC 1480020 (**3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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