Synergistic Catalysis

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Synergistic Rhodium/Phosphoric Acid Catalysis for the Enantioselective Addition of Oxonium Ylides to *ortho*-Quinone Methides

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Abstract: *We report herein a powerful and highly stereoselective protocol for the domino-type reaction of diazoesters with ortho-quinone methides generated in situ to furnish densely functionalized chromans with three contiguous stereogenic centers. A transition-metal and a Brønsted acid catalyst were shown to act synergistically to produce a transient oxonium ylide and ortho-quinone methide, respectively, in two distinct cycles. These intermediates underwent subsequent coupling in a conjugate-addition–hemiacetalization event in generally good yield with excellent diastereo- and enantioselectivity.*

The simultaneous activation of two substrates by two different catalysts that operate in concert in two distinct catalytic cycles has emerged as a powerful synthetic strategy to enable previously inefficient or even impossible chemical transformations.[1] In this field of catalysis, the combination of a transition metal and an organocatalyst has attracted particular attention, as it can provide access to entirely new reactivity patterns. Moreover, if either of the two catalysts is chiral and employed in enantiomerically pure form, such a transformation can be rendered enantioselective. In fact, quite a number of highly enantioselective synergistic transition-metal-/organocatalyzed reactions have been discovered, including Lewis acid or Brønsted acid/rhodium-cocatalyzed processes with diazo compounds.[2]

We and others have recently established Brønsted acid catalyzed, highly enantioselective conjugate-addition reactions of various nucleophiles with *ortho*-quinone methides (*o*-QMs) generated in situ.[3–6] Critical to the success of this strategy was the use of nucleophiles containing an acidic hydrogen atom capable of hydrogen bonding to a bifunctional Brønsted acid catalyst. This interaction presumably gave rise to a highly ordered transition-state assembly. Thus, enols, enamides, indoles, naphthols, and Hantzsch esters were among the most successful nucleophiles tested in these studies.[4,5]

o-QMs have also been reported to readily participate in Brønsted acid catalyzed, enantioselective oxa-Diels–Alder reactions with electron-rich dienophiles.[6] Alternatively, *o*-QMs have been prepared in situ through the fluoride-induced elimination of *ortho*-silyloxy benzyl halides and subsequently trapped with NHC-activated azolium enolates and homoenolates.[7] Apart from these processes, alkoxylation, cycloaddition, and boronate, thiol, and β-dicarbonyl addition reactions of *o*-QMs under the catalysis of palladium, BINOL, cinchona alkaloids, and bifunctional squareamides have been reported as well.[8]

The transition-metal-catalyzed decomposition of diazo compounds generates highly versatile metal carbene species, which are known to undergo a variety of transformations.[9–11] In a series of elegant studies, the research groups of Hu and Gong developed various $[Rh_2(OAc)_4]$/phosphoric acid cocatalyzed multicomponent reactions of diazoesters and alcohols or amines to furnish oxonium or ammonium ylides, respectively, as reactive intermediates, which were trapped in situ with imines[12] and glyoxylates[13] to afford highly functionalized products. These proof-of-concept studies established that rhodium and phosphoric acid catalysis can be merged to couple two distinct catalytic cycles and produce transient synthetic intermediates that persist long enough to react with each other. We wondered whether we could extend this concept to reactions of oxonium ylides obtained in situ through Rh^{II} catalysis with *o*-QMs generated in situ through phosphoric acid catalysis. We were aware that such a transformation had to outperform any competing intramolecular 1,2-proton migration of the intermediate oxonium ylide, which would result in a simple O–H-insertion product.

Herein we report the highly enantioselective conjugate addition of oxonium ylides to *o*-QMs, both of which were generated in situ. Upon hemiacetalization, the reaction gives rise to densely functionalized and highly substituted chromans. According to our design plan (Scheme 1), we reasoned that the one equivalent of water formed upon the acid-catalyzed dehydration of the starting *ortho*-hydroxy benzhydryl alcohol **1** should readily trap the rhodium carbene **I** produced in the parallel transition-metal catalysis cycle from diazoester **2**. The thus formed nucleophilic oxonium ylide **II** would now be able to undergo a conjugate addition to the *o*-QM **III** via a highly ordered transition state with the phosphoric acid bound both to the *o*-QM as well as to the oxonium ylide through two hydrogen bonds. Subsequently, the intermediate phenol **IV** could cyclize directly onto the carbonyl group in a domino-type fashion[14] to close the chroman ring system and furnish the target compound **3**.

To put these plans into practice, we started our investigations with the model reaction shown in Table 1. Benzhydryl alcohol **1a** was treated with 5 mol% each of various phosphoric acids **4** and $[Rh_2(OAc)_4]$ in chloroform at room temperature, and then a solution of ethyl 2-diazo-3-oxo-3-phenylpropanoate (**2a**) was slowly added with a syringe pump over a period of 1 h. Stirring was continued for another 6 h to

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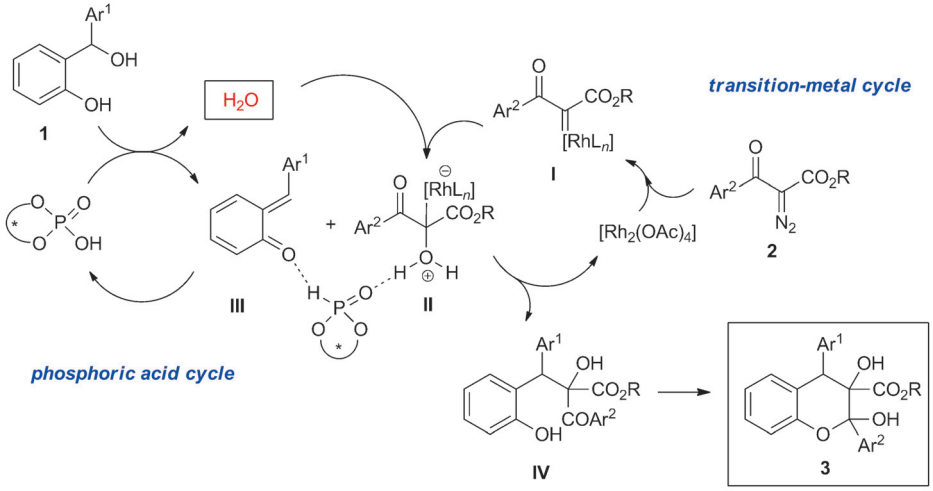


Scheme 1. Reaction design.

drive the reaction to completion. Gratifyingly, we isolated the desired chroman **3a** as a single diastereomer in 62% yield with e.r. 86:14 when phosphoric acid **4a** (R = 2,6-Me_2-4-tBuC_6H_2) was employed as the chiral Brønsted acid catalyst (Table 1, entry 1). Control experiments in the absence of either catalyst gave rise to no product formation. The structure elucidation and assignment of the relative configuration of **3a** was greatly facilitated by crystal-structure analysis[15] (see the Supporting Information).

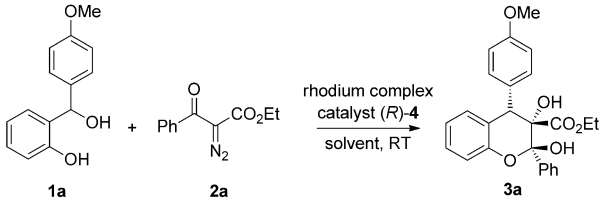
When other phosphoric acids containing bulky 3,3′-aryl groups within the BINOL backbone were used as catalysts, chroman **3a** was isolated in varying yields with varying enantiomeric ratios, again as a single diastereomer. No clear dependence of the enantioselectivity on the steric bulk of the 3,3′-substituents was observed. Notably, in some cases the opposite enantiomer was formed predominantly, in particular with sterically less encumbered phosphoric acid catalysts (Table 1, entries 2, 3, and 6). Eventually, we found the chiral phosphoric acid **4g** with 3,5-bis(trifluoromethyl)phenyl groups at the 3,3′-positions to be optimal for our reaction. With this catalyst, product **3a** was obtained as a single diastereomer in 65% yield with e.r. 96:4 (Table 1, entry 7). Various other solvents and different rhodium salts were tested, but the results were not better than that observed with $CHCl_3$ and $[Rh_2(OAc)_4]$ (Table 1, entries 8–14). Notably, however, a decrease in the amount of $[Rh_2(OAc)_4]$ used to only 2 mol% led to an enhanced yield of 87% and identical enantioselectivity (Table 1, entry 15). Lowering of the amount of the phosphoric acid catalyst from 5 to 2.5 mol%, however, resulted in a significant drop in yield and enantioselectivity (Table 1, entry 16).

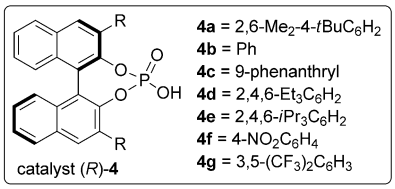
Having established optimal reaction conditions, we set out to explore the scope of this process. First, we submitted various α-diazo-β-ketoesters to this reaction (Scheme 2).[16] Generally, the reaction proceeded smoothly, and the desired products **3** were obtained as single diastereomers in good yields with excellent enantioselectivity (up to e.r. 98:2). Both electron-withdrawing and electron-donating substituents on the β-aryl group of **2** were readily tolerated in either the *meta* or *para* position. However, when an *ortho*-substituted β-aryl group was present within the diazoester, no product formation was observed, presumably for steric reasons.

We next studied the scope of this process in terms of the *o*-QM intermediate by subjecting *ortho*-hydroxy benzhydryl alcohols **1a–n** with different substituents to this process (Scheme 3). Again, in all cases studied, the reaction proceeded smoothly and was typically completed within 6–8 h at room temperature.[17]

The products **5a–n** bearing various substituents either within the *o*-QM fragment or on the β-aryl group were

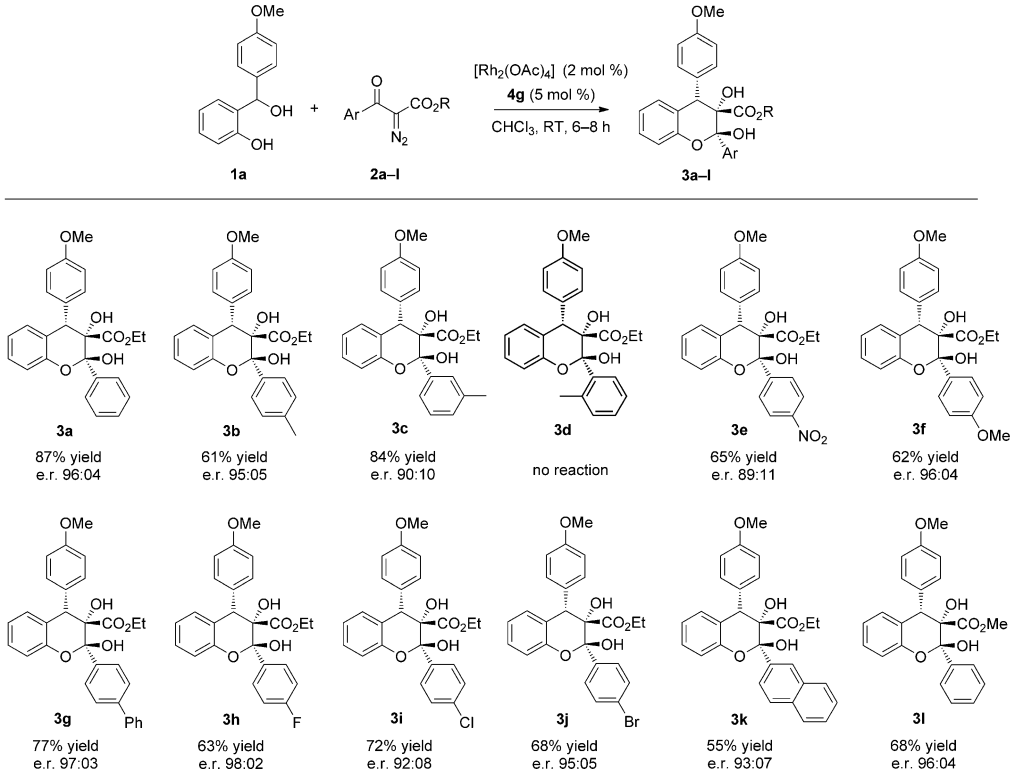
Table 1: Catalyst screening and optimization studies.[a]





Entry	Catalyst	Solvent	Rhodium complex	Yield [%]	e.r.
1	**4a**	$CHCl_3$	$[Rh_2(OAc)_4]$	62	86:14
2	**4b**	$CHCl_3$	$[Rh_2(OAc)_4]$	56	15:85
3	**4c**	$CHCl_3$	$[Rh_2(OAc)_4]$	52	21:79
4	**4d**	$CHCl_3$	$[Rh_2(OAc)_4]$	60	60:40
5	**4e**	$CHCl_3$	$[Rh_2(OAc)_4]$	62	76:24
6	**4f**	$CHCl_3$	$[Rh_2(OAc)_4]$	40	10:90
7	**4g**	$CHCl_3$	$[Rh_2(OAc)_4]$	65	96:04
8	**4g**	CH_2Cl_2	$[Rh_2(OAc)_4]$	60	86:14
9	**4g**	DCE	$[Rh_2(OAc)_4]$	48	80:20
10	**4g**	$PhCH_3$	$[Rh_2(OAc)_4]$	40	57:43
11	**4g**	PhCl	$[Rh_2(OAc)_4]$	50	65:35
12	**4g**	$CHCl_3$	$[Rh_2(CF_3COO)_4]$	40	83:17
13	**4g**	$CHCl_3$	$[Rh_2Cl_2(norb)_2]$	34	83:17
14	**4g**	$CHCl_3$	$[Rh_2(Oct)_4]$	60	81:19
15	**4g**[b]	$CHCl_3$	$[Rh_2(OAc)_4]$	87	97:03
16	**4g**[c]	$CHCl_3$	$[Rh_2(OAc)_4]$	60	83:17

[a] Reaction conditions: **1a** (0.20 mmol, 1 equiv), **2a** (0.24 mmol, 1.2 equiv), **4** (5 mol%), rhodium complex (5 mol%); **2a** was dissolved in 1 mL of the solvent and added over 1 h with a syringe pump to a solution of **1a**, **4**, and the rhodium complex in 2 mL of the solvent. [b] **1a** (0.2 mmol, 1 equiv), **2a** (0.24 mmol, 1.2 equiv), **4g** (5 mol%), $[Rh_2(OAc)_4]$ (2 mol%). [c] **1a** (0.2 mmol, 1 equiv), **2a** (0.24 mmol, 1.2 equiv), **4g** (2 mol%), $[Rh_2(OAc)_4]$ (2 mol%). DCE = 1,2-dichloroethane, norb = norbornadiene, Oct = octanoate.

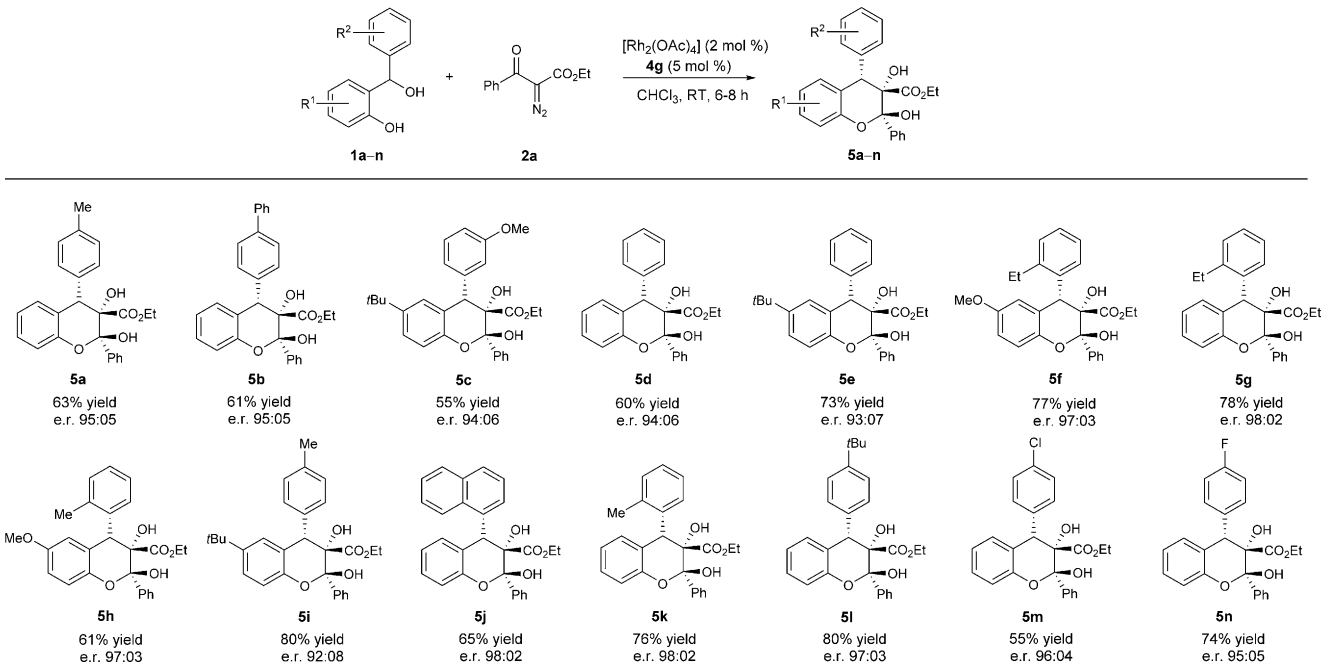


Scheme 2. Reaction of *ortho*-hydroxy benzhydryl alcohol **1a** with various diazoesters **2a–l**. Reaction conditions: **1a** (0.20 mmol, 1 equiv), **2** (1.2 equiv) dissolved in $CHCl_3$ (1 mL) and added over 1 h, **4g** (5 mol%), $[Rh_2(OAc)_4]$ (2 mol%).

obtained as single diastereomers in good yields with excellent enantiomeric ratios of up to 98:2. Further modification of the hemiacetal moiety is possible by Lewis acid catalyzed transformations.[18] Chroman **5n** gave crystals suitable for X-ray crystallography. The absolute configuration established in this way was then assigned to all other products as well (Figure 1).[15]

To obtain more insight into the reaction mechanism, we carried out a set of control experiments (Scheme 4). The addition of activated powdered 4 Å molecular sieves to the reaction mixture shut down the reaction of *ortho*-hydroxy benzhydryl alcohol **1a** with diazoester **2a**. This result clearly demonstrates the central role that generated water plays in the formation of the oxonium ylide. Furthermore, when we replaced *ortho*-hydroxy benzhydryl alcohol **1a** with its methyl ether **6**, which clearly cannot form the *o*-QM, again no product formation was observed, thus underlining the importance of the *o*-QM structure for this reaction.

Finally, we carried out the reaction with a separately prepared, isolated, and stable *o*-QM **7**[19] under the optimal



Scheme 3. Reaction of diazo ester **2a** with various *ortho*-hydroxy benzhydryl alcohols **1a–n**. Reaction conditions: **1** (0.20 mmol, 1 equiv), **2a** (0.24 mmol, 1.2 equiv) dissolved in $CHCl_3$ (1 mL) and added over 1 h, **4g** (5 mol%), $[Rh_2(OAc)_4]$ (2 mol%).

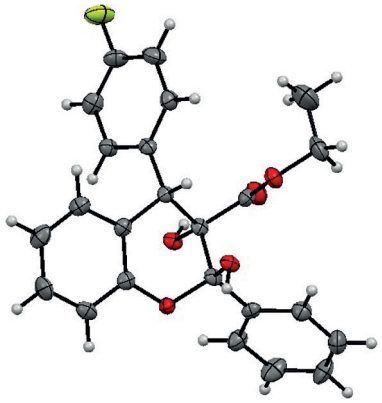
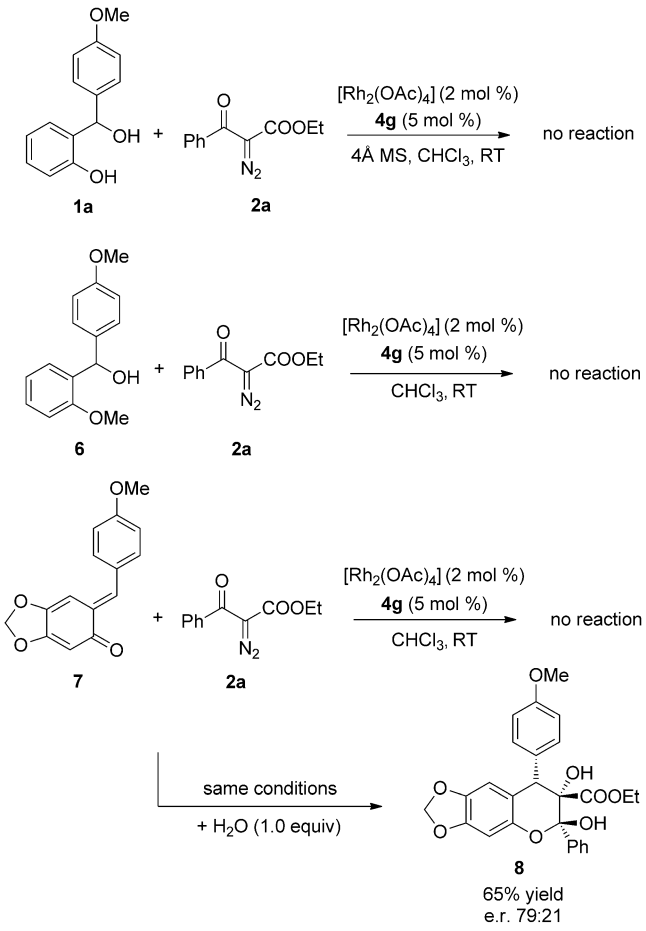


Figure 1. X-ray crystal structure of **5n**. The thermal ellipsoids are set at 50% probability.



Scheme 4. Control experiments.

reaction conditions. Again, no product was formed. However, when the same reaction was carried out in the presence of one equivalent of added water, the desired chroman **8** was obtained as a single diastereomer in 65% yield with e.r. 79:21 (Scheme 4). We believe that these experiments strongly support the proposed reaction mechanism in Scheme 1.

In summary, we have developed a highly stereoselective, synergistic rhodium/Brønsted acid catalyzed process for the conjugate addition of oxonium ylides to *o*-QMs generated in situ. Subsequent hemiacetalization of the resulting intermediates furnished densely functionalized chromans with three contiguous stereogenic centers in one synthetic step. The products, which contain two adjacent quaternary stereogenic centers and an additional tertiary stereogenic center, were formed as single diastereomers in good yields and typically with excellent enantioselectivity. A particularly striking feature of this reaction is the use of water formed as a by-product during the synthesis of the *o*-QM in the phosphoric acid cycle to trap the rhodium–carbene complex generated in the transition-metal cycle, thus furnishing the reactive oxonium ylide. Further exploration of this strategy of synergistic transition-metal/phosphoric acid catalysis with *o*-QMs is currently in progress in our laboratory.

Acknowledgements

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Keywords: *ortho*-quinone methides · oxonium ylides · phosphoric acids · rhodium · synergistic catalysis

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[15] CCDC 1428139 (**3a**) and 1428143 (**5n**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. For details concerning the crystal structures of **3a** and **5n**, see also the Supporting Information.

[16] Currently, this class of diazo compounds performs best in this process, presumably because of the enhanced stability of the derived rhodium carbenoid species.

[17] β-Substituents which do not stabilize the *o*-QM to the same extent as aryl groups, for example, alkyl groups, are currently not compatible with this process.

[18] For example, the reduction of **3a** with $BF_3{\cdot}OEt_2$ and Et_3SiH (CH_2Cl_2, −78 °C) delivered the corresponding chroman in 92% yield as a single diastereomer.

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