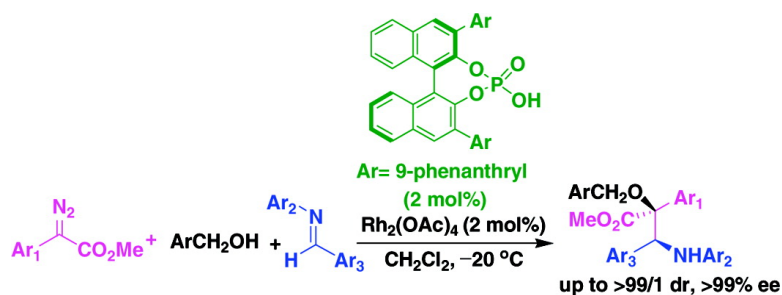


Cooperative Catalysis with Chiral Brønsted Acid-Rh(OAc): Highly Enantioselective Three-Component Reactions of Diazo Compounds with Alcohols and Imines

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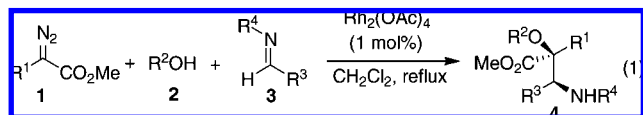
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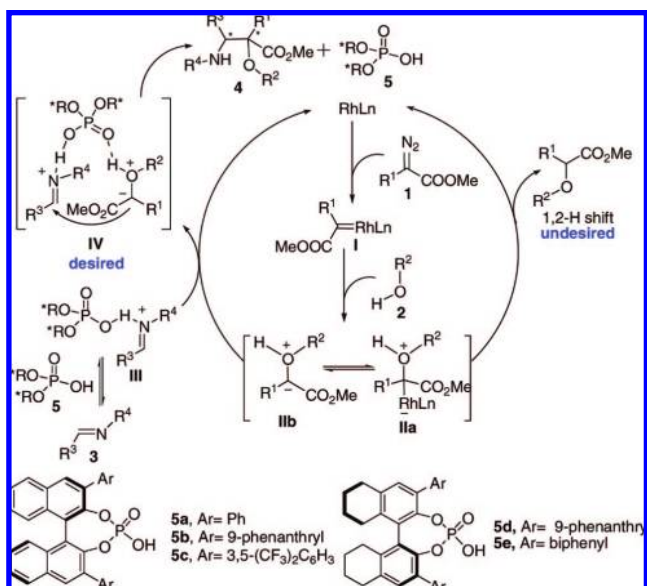
Multicomponent reactions (MCRs) offer numerous benefits over traditional chemical synthesis,¹ and catalytic enantioselective MCRs provide expedient access to chiral polyfunctional molecules. However, the development of this reaction class presents numerous challenges,^{1b,2} as transition state orientations of three or more reactants must be well controlled by a single chiral catalyst in order to achieve high enantioselectivity.

Asymmetric synthesis of β -amino- α -hydroxyl acid derivatives has attracted much attention due to both varied biological activities and their occurrences in many medicinal compounds.³ As such, efficient access to this important class of molecules with high optical purity is highly desirable. Recently, our group discovered novel three-component reactions of diazo compounds **1**, alcohols **2**, and imines **3** to afford racemic polyfunctional hydroxyl/amino acid frameworks (**4**) bearing a quaternary stereogenic center (eq 1).⁴ The reaction proceeds through oxonium ylide intermediates **IIa** or **IIb**, which are generated in situ from **1** and Rh₂(OAc)₄ (Scheme 1). These intermediates can be trapped by electrophiles such as imines. To obtain satisfactory chemoselectivity, electron-deficient imines were required to suppress an O–H insertion side product. Herein, we report the development of a catalytic asymmetric version of the three-component reaction of aryldiazoacetates, alcohols, and imines. The reaction employs a novel cooperative catalysis strategy by Rh₂(OAc)₄-initiated generation of oxonium ylide intermediates and chiral Brønsted acid activation of the imine electrophile, leading to efficient synthesis of chiral β -amino- α -hydroxyl acid derivatives with excellent enantioselectivities.



The ability of a metal complex and an organic molecule to cooperatively catalyze a chemical reaction may broaden the reaction scope within organic synthesis. Recently, this strategy has been shown to be effective in asymmetric catalysis.⁵ In the course of research in our laboratories, we observed that the aforementioned Rh₂(OAc)₄-catalyzed three-component reaction (eq 1) was accelerated by proton donors. This observation, coupled with the recent success of chiral phosphoric acids in promoting asymmetric addition reactions to imines,⁶ in particular, the multicomponent reactions,⁷ led us to envision the possibility to incorporate a chiral Brønsted acid catalyst into the ylide-based three-component reaction to achieve asymmetric catalysis. As shown in Scheme 1, activated iminium **III**, formed from a chiral phosphoric acid and the imine,

Scheme 1. Proposed Reaction Mechanism of the Title Reaction

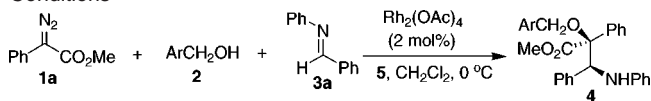


and oxonium ylide **II**, formed in situ from a diazoacetate and an alcohol initiated by a rhodium complex, would undergo an enantioselective Mannich-type reaction via proposed transition state **IV** to generate optically active **4** (Scheme 1).

To validate our hypothesis, we carried out a catalytic asymmetric three-component reaction using chiral phosphoric acid **5a**. Methyl phenyldiazoacetate **1a** was added to a mixture of benzylic alcohol **2a** and imine **3a** in the presence of rhodium acetate. We were gratified to find that the desired product, **4a**, was obtained in 84% isolated yield, 81:19 dr, and 53% ee, favoring the *syn*-isomer (Table 1, entry 1). In contrast, a control experiment of the same reaction in the absence of rhodium acetate resulted in total recovery of starting materials, indicating that phosphoric acid **5a** alone was unable to catalyze the reaction.⁸ To improve stereoselectivity, various reaction conditions were optimized. The identity of the alcohol component (**2**) was found to have significant effects on both diastereo- and enantioselectivity (entries 2–6). The use of bulky alcohols increased the dr value to 99:1 and the ee value to greater than 80% (entries 5–6). The evaluation of various chiral phosphoric acids derived from BINOL and H₈-BINOL (**5a**–**e**) revealed that 9-phenanthryl-derived catalyst **5b** was optimal, affording the *syn*-product with greater than 90% ee (entries 7–10). Notably, catalyst loadings could be decreased to 2 mol % without a deleterious effect on the reaction yield or selectivity (entry 11 vs 7). The best results were obtained at –20 °C, providing **4e** in 86% yield, >99:1 dr, and 93% ee (entry 12).

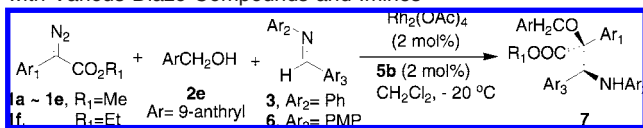
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Table 1. Catalyst Screening and Optimization of Reaction Conditions^a

entry	2 (Ar)	4	catalyst (mol %)	yield (%) ^b	dr ^c	ee (%) ^d
1	2a (Ph)	4a	5a (10)	84	81/19	56
2	2b (<i>p</i> -NO ₂ C ₆ H ₄)	4b	5a (10)	73	79/21	35
3	2c (<i>p</i> -MeOC ₆ H ₄)	4c	5a (10)	70	80/20	47
4	2d (1-naphthyl)	4d	5a (10)	89	90/10	70
5	2e (9-anthryl)	4e	5a (10)	86	>99/1	81
6	2f (9-phenanthryl)	4f	5b (5)	85	>99/1	88
7	2e (9-anthryl)	4e	5b (5)	95	>99/1	92
8	2e (9-anthryl)	4e	5c (5)	89	>99/1	77
9	2e (9-anthryl)	4e	5d (5)	78	>99/1	75
10	2e (9-anthryl)	4e	5e (5)	86	>99/1	75
11	2e (9-anthryl)	4e	5b (2)	97	>99/1	91
12 ^e	2e (9-anthryl)	4e	5b (2)	86	>99/1	93

^a Unless otherwise noted, the reaction was carried out by addition of **1a** (0.25 mmol) in CH₂Cl₂ (1 mL) to a mixture of 2 mol % of Rh₂(OAc)₄, **2** (1 equiv), **3a** (1.1 equiv), 4 Å MS (0.1 g), and **5** in 2 mL of CH₂Cl₂ under an argon atmosphere at 0 °C for 1 h. ^b Isolated yield. ^c Determined by ¹H NMR spectroscopy of the unpurified reaction mixture. ^d Determined by HPLC. ^e *T* = -20 °C.

Table 2. Enantioselective three-Component Reaction of Alcohol **2e** with Various Diazo Compounds and Imines^a

entry	1 (Ar ₁)	3 or 6 (Ar ₃)	7	yield (%) ^b	dr ^c	ee (%) ^d
1	1a (Ph)	6a (<i>m</i> -CH ₃ C ₆ H ₄)	7a	95	>99/1	90
2 ^e	1a (Ph)	6b (C ₆ H ₅)	7b	83	>99/1	94
3	1a (Ph)	6c (2,3-Cl ₂ C ₆ H ₃)	7c	95	>99/1	93
4	1a (Ph)	6d (<i>o</i> -CH ₃ C ₆ H ₄)	7d	95	>99/1	93
5	1a (Ph)	6e (<i>p</i> -CH ₃ C ₆ H ₄)	7e	92	>99/1	98
6	1a (Ph)	6f (<i>o</i> -ClC ₆ H ₄)	7f	91	>99/1	92
7	1a (Ph)	3b (<i>p</i> -BrC ₆ H ₄)	7g	87	>99/1	92
8	1a (Ph)	6g (<i>p</i> -ClC ₆ H ₄)	7h	83	>99/1	93
9	1a (Ph)	6h (<i>p</i> -BrC ₆ H ₄)	7i	82	>99/1	94
10	1a (Ph)	6i (1-naphthyl)	7j	88	>99/1	95
11	1b (<i>m</i> -BrC ₆ H ₄)	3a (C ₆ H ₅)	7k	96	>99/1	84
12	1c (<i>p</i> -MeOC ₆ H ₄)	6b (C ₆ H ₅)	7l	98	>99/1	>99
13	1c (<i>p</i> -MeOC ₆ H ₄)	6h (<i>p</i> -BrC ₆ H ₄)	7m	97	>99/1	95
14	1d (<i>p</i> -BrC ₆ H ₄)	6b (C ₆ H ₅)	7n	84	>99/1	94
15	1d (<i>p</i> -BrC ₆ H ₄)	6g (<i>p</i> -ClC ₆ H ₄)	7o	95	>99/1	92
16	1d (<i>p</i> -BrC ₆ H ₄)	3a (C ₆ H ₅)	7p	84	>99/1	92
17	1e (<i>o</i> -BrC ₆ H ₄)	6h (<i>p</i> -BrC ₆ H ₄)	7q	91	>99/1	83
18 ^f	1f (<i>trans</i> -styryl)	6h (<i>p</i> -BrC ₆ H ₄)	7r	43	>99/1	95
19	1c (<i>p</i> -MeOC ₆ H ₄)	6j (cyclohexyl)	7s	34	95/5	49

^a For conditions, see Supporting Information. ^b Isolated yield. ^c Determined by ¹H NMR spectroscopy of the unpurified reaction mixture. ^d Determined by HPLC. ^e Reaction performed on a 2.5 mmol scale with Rh₂(OAc)₄ (0.5 mol %) and **5b** (1 mol %). ^f **1f** (2 equiv) was used, *T* = 0 °C.

Under the optimized conditions, alcohol **2e** undergoes highly selective reaction with structurally diverse imines and diazo compounds (Table 2). In most cases, only *syn*-products were obtained in greater than 90% ee. Notably, one example stereospecifically provided (*S,S*)-*syn* **7l** in high yield (entry 12). Extension of aryldiazo compounds **1a–1e** to ethyl *trans*-styryldiazoacetate (**1f**) gave the desired product **7r** with moderate yield while maintaining high ee (entry 18). When imine derived from aliphatic aldehyde such as cyclohexyl formaldehyde was employed, both yield and ee dropped significantly (entry 19). Unfortunately, the reaction did not work well with ethyl diazoacetate under the current reaction conditions.

The stereochemistry of the major isomer of brominated analogue **7k** was determined to be (*2S,3S*) by single-crystal X-ray analysis, and other compounds were tentatively assigned by analogy. The 9-anthryl protecting group of the products **7** can be readily removed according to literature procedure⁹ to give free the hydroxyl analogue of **7** in good yield¹⁰ (see Supporting Information).

In summary, we have developed an enantioselective three-component reaction of diazo compounds and alcohols with imines in the presence of Rh₂(OAc)₄ and a chiral Brønsted acid. The reaction provides an efficient entry to *syn*-β-amino-α-hydroxyl acid derivatives bearing a quaternary carbon stereogenic center in high yields with excellent enantioselectivities. We anticipate that the concept of Brønsted acid–metal cooperative catalysis will be applicable to other reactions involving the addition of oxonium ylide nucleophiles to various electrophiles that can be activated by Brønsted acids. Our results to this end will be reported in due course.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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