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Brønsted Acid/Lewis Acid Cooperatively Catalyzed Addition of Diazoester to 2*H*-chromene Acetals

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Abstract

A novel Brønsted acid/Lewis acid dual catalyst system has been developed to promote an efficient C–C bond formation between a range of oxocarbenium precursors derived from chromene acetals and ethyl diazoacetate. The reaction proceeds under mild conditions and is tolerant of common functionalized 2*H*-chromene and isochromene acetals. In addition, an asymmetric variant of diazoacetate addition towards 2*H*-chromene acetal is described. Continued investigations include the further optimization of asymmetric induction towards the formation of diazo ester substituted 2*H*-chromene.

Keywords

Brønsted Acid; Lewis acid; Diazo compounds; Oxocarbenium; Enantioselectivity

Introduction

In situ generated, highly reactive oxocarbenium ions are useful intermediates for the synthesis of complex ether-containing compounds.¹ Oxocarbenium chemistry offers numerous possibilities in the synthesis of natural products and pharmaceuticals.² In particular, resonance-stabilized chromene and isochromane derivatives have been accessed by trapping of oxocarbenium precursors.³ Jacobsen and co-workers designed an elegant chiral anion binding approach for the thiourea catalyzed asymmetric addition of enoxysilanes to chloroisochromans.⁴ Schaus reported the reaction between boronates and 2*H*-chromene acetals to form 2-vinyl- and 2-aryl-2*H*-chromenes in high yield and enantioselectivity (Scheme 1).⁵ Rueping reported a synergistic catalytic system for the first asymmetric addition of aldehydes to in-situ generated prochiral oxocarbenium ions employing an enamine catalyst (Scheme 1).⁶ Furthermore, metal-mediated nucleophilic addition to oxocarbenium has also been reported. The recent work of Doyle illustrates a Ni(0) promoted C–C bond formation between 2*H*-chromene acetals and boronic acid in a

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Supporting Information (see footnote on the first page of this article): General experimental remarks, experimental details and spectra of the products.

racemic fashion, which tolerates a wide variety of boronic acids.⁷ Watson developed an enantioselective Cu(I)-catalyzed addition of terminal alkynes to isochroman acetal.⁸

BINOL-phosphoric acid has emerged as a powerful chiral Brønsted acid catalyst in many C–C bond-forming reactions. Akiyama⁹ and Terada¹⁰ pioneered the study of chiral BINOL-derived phosphoric acids in Mannich-type reactions and aza-Friedel–Crafts alkylation. The development of novel organic transformations promoted by BINOL phosphoric acid and its derivatives has been continuously studied in recent years.¹¹ List has utilized BINOL phosphate for a variety of asymmetric reactions.¹² Boronate was utilized as a nucleophile by Antilla for asymmetric addition using BINOL-phosphoric acid as the catalyst.¹³ Several novel organic transformations were developed by using BINOL-phosphoric acid under various reaction conditions.¹⁴ α -Unsubstituted diazocarbonyl compounds, which are generally considered as carbene precursors,¹⁵ can be coupled with various electrophiles as nucleophiles,¹⁶ such as aldehydes¹⁷ and imines¹⁸ with the retention of diazo moiety under Brønsted acid catalyzed reaction conditions. However, to the best of our knowledge, the use of nucleophilic diazoacetates in additions to oxocarbeniums has not been reported.

Herein, we report the development of a new dual catalyst system using both BINOL-phosphoric acid and Lewis acid,¹⁹ which enables the reaction of diazoacetate with benzocyclic acetals. This methodology provides access to a class of C2-substituted chromenes, which are present in many bioactive natural products.²⁰ The optimized reaction conditions are mild and can tolerate a variety of functional groups to generate the products in excellent yields. The diazoacetate addition can be rendered asymmetric utilizing chiral BINOL-phosphoric acid and decent enantioselectivity was achieved together with good yield of diazo ester substituted 2*H*-chromene.

Results and Discussion

We initiated our study by investigating the addition of ethyl diazoacetate **6** to 2-ethoxy-2*H*-chromene **5a** (Table 1). The diazoacetate addition product **7a** can act as the synthetic intermediates for the synthesis of bioactive compounds, such as deoxyerythrostominone²¹ and (*S,R,R,R*)-nebevivolol.²² The control reaction showed that the addition reaction could not occur without both Brønsted acid and Lewis acid (Table 1, entry 1). The use of previously successful tartaric acid in a racemic form, in combination of catalytic amount of Yb(OTf)₃, provided the desired addition product **7** in modest yields (Table 1, entry 2). Amino-acid such as L-proline **2**, which is a powerful catalyst in organocatalysis, only resulted in low reactivity (Table 1, entry 3). Thiourea catalyst **3** was more successful at promoting the diazo addition reaction affording the product in 66% yield (Table 1, entry 4). Alternatively, BINOL (1,1'-bi-2-naphthol) derived phosphoric acid (BINOL-phosphoric acid **4**), together with Yb(OTf)₃, provided the highest yield in the addition reaction (Table 1, entry 5) and was selected as the catalyst for further investigation. The addition reaction did not proceed in the absence of Brønsted acid, which indicates the crucial role of the BINOL-phosphoric acid in this reaction (Table 1, entry 6). Furthermore, the utilization of BINOL-phosphoric acid **4** without Yb(OTf)₃ Lewis acid gave decent yield of the desired diazo chromene product (Table 1, entry 7). This observation suggested that the utilization of Yb(OTf)₃ enhanced the reaction rate, which results in high yield of the desired product. However, significant decrease

in yield was observed when the reaction was run at 0 °C (Table 1, entry 8). As a result, the rest of this study was conducted under room temperature. It is concluded that the addition reaction was promoted by Brønsted acid and the reaction rate was further enhanced by the Lewis acid. *n*-Butyl and isopropyl derived acetals **5b** and **5c** were synthesized as alternative oxocarbenium precursors. However, only lower yields were observed under the standard reaction conditions of these bulkier acetals (Table 1, entries 9 and 10). Solvent effects were also investigated under the optimal reaction conditions with BINOL-phosphoric acid **4** and 2-ethoxy-2*H*-chromene acetal **5a**. A solvent screen indicated that CH₂Cl₂ was the best solvent among other common organic solvents (Table 1, entries 4 and 11-14). Chloroform and toluene gave comparable yields (Table 1, entries 11 and 12), and THF and methanol gave lower yields, presumably due to unfavorable interactions with the catalysts or inhibition of oxocarbenium formation (Table 1, entries 13-14).

Encouraged by these preliminary results, we further extended this methodology to a variety of substituted 2*H*-chromene acetals. The optimized reaction proved to be general for a range of 2*H*-chromene acetals (Table 2). This reaction proceeded smoothly with chromene acetal **5a**, furnishing diazoacetate substituted 2*H*-chromene **7a** in good yield (Table 2, entry 1). Methyl substituted chromene acetal **5b** provided the desired product in good yield (Table 2, entry 2). Reaction with electron-rich chromene acetal **5c** proceeded smoothly within 1 h, despite the fact that 7-methoxy substituted chromene acetal **5c** tends to decompose in the presence of strong Brønsted acid over time (Table 2, entry 3). 6,7-dioxo-2*H*-chromene acetal **5d** also underwent this reaction well with slightly compromised yield (Table 2, entry 4). Halogenated chromene acetals **5e** and **5f** were transformed to the desired diazo ester substituted chromenes in good yields (Table 2, entries 5 and 6). Electron-deficient chromene acetal **5g** underwent the reaction in the same fashion, providing desired product **7g** in good yield at extended reaction times under room temperature (Table 2, entry 7).

We next tested whether the reaction could be extended to the diazo addition of isochromene acetal **8**. Under the optimal reaction condition for diazo oxocarbenium addition, the reaction with an isochromene acetal proceeded in a promising 76% yield (Figure 1). This result provides a preliminary indication of the utility of the catalytic methodology and the possibility to expand this strategy to other cyclic oxocarbenium ions.

At last, we sought to develop an asymmetric variant of the diazo addition reaction using a chiral Brønsted acid (Table 3). Chiral acid catalyst, such as (+)-tartaric acid or *L*-proline failed to afford any enantioselectivity. We initiated our investigation by evaluating the reaction of ethyl diazoacetate **6** with 2*H*-chromene acetal **5a** in the presence of chiral BINOL-phosphoric acid catalysts. Unsubstituted BINOL-phosphoric acid afforded the product in very low yield (Table 3, entry 1). 3,3'-Dibromo-substituted BINOL-phosphoric acid **10b** afforded the product in good yield and modest enantioselectivity (Table 3, entry 2). 3,3'-Aryl-substituted catalysts **10c-f** afforded similar or lower selectivities (Table 3, entries 3-6). Bulky catalysts with silyl and anthracenyl substitutions at C3 position were also evaluated but gave only marginal improvement in selectivity (Table 3, entries 8-9). Finally, the commercially available (*S*)-TRIP catalyst **10i** afforded the desired product in the highest yield (81:19, Table 3, entry 9). Further solvent screens indicated that toluene gave the highest selectivity (Table 3, entries 10-13).

Conclusions

In summary, we have developed the first asymmetric addition of diazo acetate to prochiral oxocarbenium ions yielding valuable chiral 2*H*-chromene scaffolds. A catalytic system consisting of an achiral Lewis acid and a Brønsted acidic phosphoric acid catalyst was the key to affording the products in good yields. Asymmetric versions of this reaction are available by using commercially available chiral phosphoric acids. Further studies to expand the scope and utility of the reaction are ongoing.

Experimental Section

General Information

All ^1H NMR, and ^{13}C NMR spectra were recorded using Varian Unity Plus 400 or 500 MHz spectrometer at ambient temperature in CDCl_3 . Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, and integration. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR ESP spectrophotometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and were reported as $[\alpha]_{\text{D}}$ (concentration in grams/100 mL solvent). Chiral HPLC analysis was performed using an Agilent 1100 series HPLC System with a diode array detector. Chiral columns include Chiralcel®OD (Chiral Technologies Inc., 25cm×4.6mm I.D.), Chiralpak®AD-H (Chiral Technologies Inc., 25cm × 4.6 mm I.D.) and (*R,R*)-Whelk-O (Regis®Technologies Inc., 25cm × 4.6 mm I.D.). Analytical thin layer chromatography was performed using EMD 0.25 mm silica gel 60-F plates. Flash column chromatography was performed on Sorbent Technologies 60 Å silica gel.

Procedure for the dual acid-catalyzed addition of ethyl diazoacetate **6** to 2-ethoxy-2*H*-chromene **5a**

To a flame-dried 5 mL round-bottom flask equipped with stir bar and rubber septum under Ar was added $\text{Yb}(\text{OTf})_3$ (15.5 mg, 0.025 mmol, 5 mol%), BINOL-phosphoric acid (34.8 mg, 0.1 mmol, 20 mol%), ethyl diazoacetate **6** (78.4 mg, 0.6 mmol, 1.2 equiv. with 20% of CH_2Cl_2) and CH_2Cl_2 (2.5 mL). Then the chromene acetal **5a** (88.0 mg, 0.5 mmol, 1.0 equiv.) was added and the reaction was stirred vigorously for 12 h at room temperature. The reaction was purified without work-up by flash chromatography over silica gel column (2% EtOAc in hexanes) to afford the diazo addition product **7a** as a yellow oil (97 mg, 0.42 mmol, 83% yield). The product **7a** can be stored at $-20\text{ }^\circ\text{C}$ in the dark for up to two months without decomposition of the structure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
2*H*-chromene acetal addition reaction.

Figure 1.
Nucleophilic addition to isochromene acetal **8**.

Table 1

Reaction optimizations^[a].

Entry	Catalyst	Lewis acid	R	Solvent	Yield ^[b]
1	-	-	Et (5a)	CH ₂ Cl ₂	0%
2	1	Yb(OTf) ₃	Et (5a)	CH ₂ Cl ₂	40%
3	2	Yb(OTf) ₃	Et (5a)	CH ₂ Cl ₂	11%
4	3	Yb(OTf) ₃	Et (5a)	CH ₂ Cl ₂	66%
5	4	Yb(OTf) ₃	Et (5a)	CH ₂ Cl ₂	82%
6	-	Yb(OTf) ₃	Et (5a)	CH ₂ Cl ₂	<5%
7	4	-	Et (5a)	CH ₂ Cl ₂	58%
8 ^[c]	4	Yb(OTf) ₃	Et (5a)	CH ₂ Cl ₂	42%
9	4	Yb(OTf) ₃	<i>n</i> Bu (5b)	CH ₂ Cl ₂	74%
10	4	Yb(OTf) ₃	<i>i</i> Pr (5c)	CH ₂ Cl ₂	63%
11	4	Yb(OTf) ₃	Et (5a)	CHCl ₃	78%
12	4	Yb(OTf) ₃	Et (5a)	PhCH ₃	80%
13	4	Yb(OTf) ₃	Et (5a)	THF	54%
14	4	Yb(OTf) ₃	Et (5a)	CH ₃ OH	12%

^[a] Reaction conditions: 0.5 mmol of acetal **5**, 0.6 mmol of ethyl diazoacetate **6**, 20 mol-% Brønsted acid catalyst, 0.2 M in the solvent for 12 h at room temperature.

^[b] Isolated yield.

^[c] at 0 °C

Table 2

2*H*-chromene acetal evaluation^[a].

Entry	Substrate	Product	Yield ^[d]
1			82%
2			83%
3 ^[b]			75%
4 ^[b]			71%
5			70%
6			72%
7 ^[c]			76%

^[a] Reaction conditions: 0.5 mmol of **5**, 20 mol-% catalyst **4**, 0.2 M in the solvent for 12 h at room temperature.^[b] 1 h.^[c] 24 h.^[d] Isolated yield.

Table 3

The stereoselective nucleophilic addition reaction of **6** using chiral phosphoric acid.^[a]

Entry	Catalyst	Solvent	Yield ^[b]	e.r. ^[c]
1	10a	PhCH ₃	81%	52:48
2	10b	PhCH ₃	75%	65:35
3	10c	PhCH ₃	71%	55:45
4	10d	PhCH ₃	76%	56:44
5	10e	PhCH ₃	72%	56:44
6	10f	PhCH ₃	87%	65:35
7	10g	PhCH ₃	66%	55:45
8	10h	PhCH ₃	76%	68:32
9	10i	PhCH₃	82%	81:19
10	10i	PhCF ₃	82%	78:22
11	10i	CH ₂ Cl ₂	83%	63:37
12	10i	Et ₂ O	54%	65:35
13	10i	THF	55%	75:25

^[a] Reaction conditions: 0.5 mmol of **5a**, 20 mol-% chiral catalyst, 0.2 M in the solvent for 12 h at room temperature.

^[b] Isolated yield.

^[c] Determined by HPLC.