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Diastereoselective synthesis of isochromans via the Cu(II)-catalysed intramolecular Michael-type trapping of oxonium ylides[†]

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A highly diastereoselective approach for the rapid construction of an isochroman skeleton was achieved by the copper(\square)-catalyzed transformation of alcohol-tethered enones and diazo compounds. This transformation was proposed to proceed through the intramolecular Michael-type trapping of an *in situ* generated oxonium ylide intermediate. The copper(\square) catalyst may play a dual role in catalyzing diazo decomposition as well as activating the enone unit. With this method, a series of 3,4-substituted isochromans were obtained with excellent diastereoselectivities under very mild reaction conditions.

The synthesis of heterocycles has drawn a large amount of attention in organic chemistry due to their abundance in a majority of natural products and drugs.¹ Achieving heterocyclic cores through multiple bond formation in a single step has always been in great demand owing to its highly step-economic features.² Over the past decade, in situ trapping of active intermediates derived from metal carbenes has been developed into a powerful strategy for different types of Multi-Component Reactions (MCR).³⁻⁸ In this context, by applying this interception strategy in an intramolecular manner starting from alcohol or amine substrates tethered with electrophilic units, an array of diazo-involved cyclization reactions has been developed to effectively construct different types of heterocyclic skeleton (Scheme 1A).9 Among them, expensive rhodium catalysts are essential for metal carbene formation, and co-catalysts are generally required for the activation of the electrophilic unit to enable the trapping process, and aldol-type trapping

^a Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, School of Chemistry and Molecular Engineering, East China Normal University, 3663 North Zhongshan Rd., Shanghai, 200062, China. with carbonyl electrophiles is predominant due to a wide choice of activating catalysts. In view of the high efficiency of this strategy, a novel reaction design by incorporating new types of electrophilic units, as well as developing more efficient catalytic systems to allow for the rapid construction of heterocycles with structural diversity, is highly sought after.

Isochroman cores constitute the framework of a variety of bioactive natural products.¹⁰ Examples include penicisochromans D and E from *Penicillium PSUF40*,^{11a} pergillin from *Aspergillus ustus*,^{11b} blapsin B from *Blaps japanensis*,^{11c} and tezettine from *Pancratium maritimiim* (Scheme 1C).^{11d} As a result, different approaches have been developed for the synthesis of isochroman skeletons.¹² As a result of our continuous research efforts in designing new metal carbene-involved transformations for



Scheme 1 Heterocycle synthesis by the intramolecular trapping of onium ylides and the design for the rapid construction of isochromans.

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heterocycle synthesis, an efficient method for the synthesis of 3,4-substituted isochromans starting from alcohol-tethered enones and diazo compounds via a transition metal-catalyzed cyclization process could be envisioned (Scheme 1B). The intramolecular Michael-type trapping of an in situ generated oxonium ylide intermediate derived from metal carbene is anticipated to fulfill such a process. To achieve this goal, several difficulties need to be considered: (1) the in situ generated oxonium ylide intermediate may undergo rapid 1,2-proton transfer before it can be intercepted by the tethered enone unit;³ (2) an intramolecular oxo-Michael addition of the alcohol-tethered enone under metal catalysis may occur to afford isobenzofurans;¹³ (3) Michael-type trapping of oxonium ylide intermediates with enones is difficult owing to their relatively low electrophilic features compared with carbonyl compounds.¹⁴ Herein, we report our recent results on a copper-catalyzed cyclization reaction between alcohol-tethered enones and diazo compounds for the efficient construction of isochroman derivatives.

Initially, an alcohol-tethered enone **1a** was chosen as the model substrate to react with methyl phenyldiazoacetate **2a** by employing different metal catalysts. When 1 mol% of $Rh_2(OAc)_4$ was employed, the desired cyclization product **3a** was obtained in 21% yield with good diastereoselectivity, as well as the O–H insertion product **4** in 65% yield (Table 1, entry 1). Realizing that Rh(II) might be too reactive for the O–H insertion pathway, several other types of metal catalyst were tested. Among them, $[Pd(allyl)Cl]_2$ showed a similar catalytic effect (Table 1, entry 2),

Table 1 Condition optimization ^a					
L la	N2 Ph 2a OH catalyst (10 mol%) rt, 12 h Ph	O Ph Bh 3a	O ₂ Me	Ph O CO ₂ Me CO ₂ Me Ph 4	C Ph 5
Entry	Catalyst	Solvent	Yield of $3a^{b}$ (%)	d.r. of 3a ^c	Yields of $4/5^b$ (%)
1	$Rh_2(OAc)_4^d$	CH_2Cl_2	21	90:10	65/<5
2	[Pd(allyl)Cl]2 ^e	CH_2Cl_2	34	90:10	51/<5
3	FeTPPCI	CH_2Cl_2	<5	_	< 5/< 5
4	Cu(CH ₃ CN) ₄ PF ₆	CH_2Cl_2	60	95:5	< 5/< 5
5	CuCl	CH_2Cl_2	< 5		< 5/< 5
6	CuSO ₄	CH_2Cl_2	35	95:5	< 5/< 5
7	$Cu(OTf)_2$	CH_2Cl_2	63	95:5	$15/\!<\!5$
8	$Cu(OTf)_2$	DCE	51	95:5	< 5/10
9	$Cu(OTf)_2$	$CHCl_3$	44	95:5	< 5/20
10	$Cu(OTf)_2$	Toluene	25	95:5	< 5/< 5
11	$Cu(OTf)_2$	EtOAc	16	95:5	< 5/< 5
12^{f}	$Cu(OTf)_2$	CH_2Cl_2	78	95:5	< 5/5
$13^{f,g}$	$Cu(OTf)_2$	CH_2Cl_2	81	95:5	< 5/< 5
$14^{f,g}$		CH_2Cl_2	< 5		< 5/< 5

^{*a*} Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (10 mol%), 4 Å MS (150 mg), solvent (2.5 mL), r.t., 12 h. ^{*b*} Isolated yields; "<5%" means the product was not observed by ¹H NMR of crude mixture. ^{*c*} Determined by ¹H NMR of crude mixture. ^{*d*} 1 mol%. ^{*e*} 2 mol%. ^{*f*} Reaction at 40 °C. ^{*g*} **2a** (0.5 mmol).

FeTPPCl showed no catalytic activity at all (Table 1, entry 3), and the use of Cu(CH₃CN)₄PF₆ was promising, yielding the desired cyclization product 3a in 60% yield with excellent diastereoselectivity and the undesired O-H insertion product was not observed (Table 1, entry 4). Several other copper catalysts were then tested. The reaction did not proceed when CuCl was used (Table 1, entry 5). It was promising to find that the much cheaper CuSO₄ salt also catalysed this reaction, albeit with a reduced efficiency (Table 1, entry 6). The reaction efficiency was further improved by employing Cu(OTf)₂ as the catalyst (Table 1, entry 7). Different solvents were then screened, and CH₂Cl₂ was proven to be the most optimal. With other types of halogenated solvents such as DCE and CHCl₃, this transformation was less effective and the undesired oxo-Michael addition product 5 derived from 1a was observed (Table 1, entries 8 and 9). Toluene and EtOAc also gave poor yields of 3a (Table 1, entries 10 and 11). When the reaction temperature was raised to 40 °C, 3a was obtained exclusively in 78% yield and the stereoselectivity remained excellent (Table 1, entry 12). Increasing the amount of 2a was helpful for suppressing the formation of 5 and therefore further improved the yield of 3a to 81% (Table 1, entry 13). The absence of a copper catalyst led to no consumption of both starting materials, indicating its indispensable role for the current transformation (Table 1, entry 14).

With the optimized reaction conditions in hand, the substrate scope was investigated (Scheme 2). First, a series of aryl diazo esters bearing different substituents on the aryl ring were tested. Different halogen substituents including F, Cl and Br could be tolerated regardless of their electronic effects, yielding the corresponding isochroman products in good yields (3b-3e and 3j). Several diazo esters bearing electron-donating substituents on the aryl ring, including those bearing bis- and tris-substituents, also underwent the desired cyclization to afford the isochroman products in moderate to good yields (3g-3i, 3k and 3l). Substrates bearing electronically distinct substituents on the aryl rings of the enone unit were then investigated. The electronic features of the different substituents showed less impact, and the corresponding cyclization products were obtained in moderate to good yields (3n-3t). Alkyl substituents on the enone unit were also tolerated, affording the isochroman product in moderate yield (3u). Substrates with secondary alcohol units also worked well to give the corresponding cyclization product in good yield (3v) with a 1:1 dr. It is worth mentioning that all of the isochroman products showed excellent diastereoselectivities to yield the cyclization products as single diastereomers except for 3v, which showed a 1:1 dr. This transformation is currently limited to the use of donor/acceptor type aryldiazoacetates as the diazo source, and a number of other types of diazo compounds all failed to give the desired cyclization product.15 Replacing the enone unit with other types of Michael acceptor, such as ester or cyano groups, also failed to produce the corresponding cyclization product.¹⁵ Finally, the structure and stereochemistry of the products were unambiguously confirmed by the single crystal X-ray analysis of 3a, which was concluded to be syn. The analogous



Scheme 2 Substrate scope.





To shed light on the mechanism of this transformation, two control experiments were conducted. First, the O-H insertion product 4 derived from 1a and 2a was subjected to standard reaction conditions, but the cyclization product 3a was not observed even after 24 h (eqn (1)). This result indicated that a stepwise pathway involving an O-H insertion followed by an intramolecular Michael reaction is unlikely for the current transformation. On the other hand, the oxo-Michael adduct 5 from 1a was allowed to react with 2a under standard reaction conditions, and 3a was also not observed (eqn (2)). This result indicated that 5 was not the intermediate for the formation of 3a. Moreover, the absence of a copper catalyst showed no consumption of 1a (the formation of 5 can only be achieved when in the presence of a copper catalyst, eqn (3)), indicating that the copper catalyst may play a dual role in catalyzing diazo decomposition as well as activating the enone unit in the following Michael addition.

Based on these results and the precedent reports, a plausible mechanism was proposed (Scheme 3). Diazoacetate 2a was first converted into copper carbene A, which then reacted with 1a to afford oxonium ylide B. This oxonium ylide could be further isomerized into its more stable enolate form C. The O-H insertion product 4 was generated via 1,2-proton transfer with this active intermediate (path A). On the other hand, in the presence of a tethered enone unit, intramolecular Michael-type trapping of intermediate C would occur to afford the cyclization product 3a (path B). To rationalize the excellent diastereoselectivity observed for this transformation, a transition state for the intramolecular Michael-type trapping step was proposed. Intramolecular hydrogen-bonding between the oxygen atom on the enolated ylide and the proton derived from the benzyl alcohol may play a key role in pushing the enone unit away, to therefore generate the syn-product preferentially (Scheme 3).

To further illustrate the practical applicability of this protocol, a gram-scale reaction was conducted. With 5 mol% of loaded catalyst, 4.2 mmol of **1a** underwent the desired cyclization to provide 1.2 g of **3a** in 71% yield (Scheme 4a). To establish the



Scheme 3 Proposed mechanism and explanation of the stereochemistry.



Scheme 4 Gram-scale synthesis of **3a** and its synthetic applications.

synthetic significance of this transformation, the isochroman product **3a** was transformed into different analogues (Scheme 4b). Thus, simple hydrolysis resulted in carboxylic acid **6** in excellent yield.¹⁷ Fischer-indole synthesis afforded the indole substituted isochroman 7 in moderate yield and the diastereoselectivity was completely maintained.¹⁸ Furthermore, reduction followed by FeCl₃-mediated regioselective annulation resulted in a tetracyclic molecule **8** bearing 3 stereocenters in good yield with high diastereoselectivity.¹⁹

In conclusion, we have developed a highly diastereoselective approach for the synthesis of 3,4-substituted isochromans by the copper(π)-catalyzed cyclization reaction of alcohol-tethered enones and diazo compounds. This transformation was proposed to proceed through the intramolecular Michael-type trapping of an *in situ* generated oxonium ylide intermediate. The less expensive copper(π) catalyst played a key role in carbene formation, enone activation and selectivity control in this transformation. Further application of this strategy to the construction of heterocycles with structural diversity is in progress.

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Conflicts of interest

There are no conflicts to declare.

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