Domino Reactions

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Highly Diastereoselective Multicomponent Cascade Reactions: Efficient Synthesis of Functionalized 1-Indanols**

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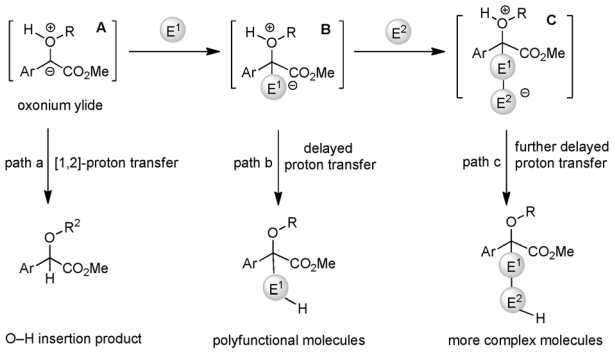
The rapid formation of complex molecules from simple materials constitutes a great challenge in modern organic chemistry and drug discovery.[1] Multicomponent reactions (MCRs) provide a highly efficient approach for the preparation of polyfunctional molecules from simple starting materials in an operationally simple and atom-economical manner.[2] Cascade or domino reactions represent a powerful chemical tool to build rather complex molecules, for example, complex ring systems that bear multiple stereogenic centers in an efficient and highly stereoselective manner.[3] However, in most cases, multiple steps are required to form precursors for cascade or domino reactions.[4] The combination of multicomponent reactions and cascade processes in one system would enable the preparation of multifunctional, highly complex ring systems in the least number of synthetic steps.[5]

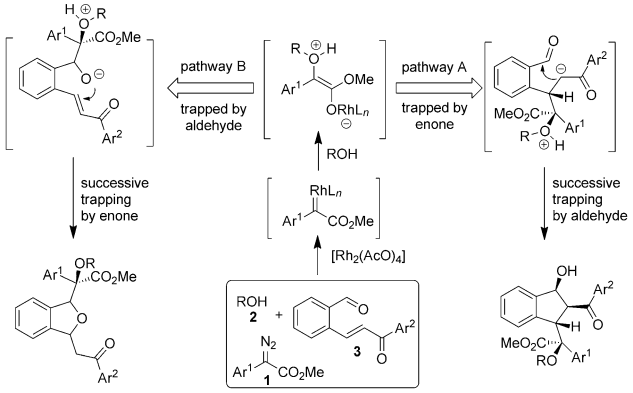
It is well known that protic oxonium ylide **A**, which can be generated in situ from a diazo compound and an alcohol, will easily lead to a traditional O–H insertion product through an extremely fast [1,2]-proton-transfer process (Scheme 1, path a).[6] Excitingly, we were recently able to trap the in situ generated protic oxonium ylide **A** by electrophiles or electrophilic groups to form intermediate **B** and, followed by a "delayed proton transfer", to build complex molecules with multifunctional groups (Scheme 1, path b).[7] Using this strategy, polyfunctional bioactive molecules can be rapidly formed through this method.[8] The chemoselectivity and stereoselectivity of the desired reaction can be well controlled, especially by applying cooperative catalysis.[9]

In the course of our studies, we were interested to find out whether the protic zwitterionic intermediate **B** can be trapped by additional electrophiles or electrophilic groups prior to the "delayed proton transfer" process. The additional trapping process will provide an opportunity to discover new transformations to generate a more diversified structural motif in one step (Scheme 1, path c). Owing to the involvement of the additional trapping process, this strategy may also be used to rationally design new multicomponent cascade reactions.



Scheme 1. Design of new cascade or domino reactions of successive trapping active intermediates through delayed proton transfer. E^1, E^2 = electrophiles or electrophilic groups.

We first considered the second trapping process as a step in an intramolecular cascade reaction. In our approach, we used key precursor **3**, which bears bifunctional electrophilic groups, that is, formyl and enone moieties, and which was used by Baba and co-workers[10] as a starting material in their cascade reactions, as the third component to trap the oxonium ylide. Precursor **3** was easily prepared by condensation of *ortho*-phthalaldehyde with the corresponding Wittig reagent, and obtained in good yield (70–85%). Two possible reaction pathways are involved in the trapping process of the alcoholic oxonium ylide (Scheme 2). First, the enone functionality may trap the oxonium ylide to form the corresponding zwitterionic intermediate, followed by an intramolecular Aldol-type reaction to afford functionalized indanol derivatives (pathway A). Alternatively, the oxonium ylide may first be trapped by the formyl group, followed by an aza-Michael addition that



Scheme 2. Two main possible reaction pathways of trapping oxonium ylide by **3**. L = ligand.

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leads to 1,3-dihydroisobenzofuran derivatives (pathway B). Both 1-indanol derivates and 1,3-dihydroisobenzofuran derivatives are found in natural products and many biologically active and pharmaceutically important molecules.[11]

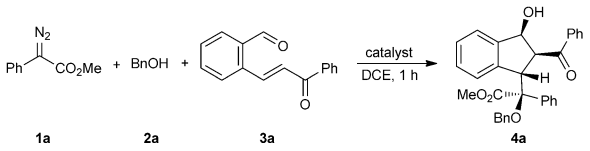
We started our investigations by employing compound **3a** to trap the oxonium ylide that was generated in situ in the reaction of methyl phenyldiazoacetate **1a** and benzyl alcohol **2a** in the presence of a transition-metal catalyst. $Cu(OTf)_2$ was the best catalyst for the Michael-type trapping of oxonium ylides by enones as electrophilic trapping agents,[12] and was thus first employed to catalyze this reaction. No desired product, but a significant amount of side-product from O–H insertion was observed (Table 1, entry 1). When $[Rh_2(OAc)_4]$ was used as the catalyst instead of $Cu(OTf)_2$, the reaction went smoothly via pathway A to give product **4a** of a Michael-aldol-type reaction in 72% yield with a d.r. > 20:1 (Table 1, entry 2). Even though we discovered that oxonium ylides can be successfully trapped by aldehydes,[7b,9a] ketones[7a] and imines,[7c,9a–c] only a few examples have been reported of the use of enones as electrophiles to trap oxonium ylides.[12,13] The preference of pathway A over pathway B under the present reaction conditions is possibly due to the second intramolecular Aldol-type trapping process, which is the driving force that facilitates the first trapping process. As a result, polyfunctional complex molecules with four new bonds and a new ring system were rapidly generated through this one-pot cascade reaction.

In order to optimize the reaction conditions, additional catalysts were surveyed. Complexes $[Cu(hfaa)_2]$ and $[RuCl_2(C_{10}H_{14})]$ also gave the desired product **4a** in 45% and 68% yield, respectively (Table 1, entries 3 and 4). The effect of solvents and the reaction temperature was also investigated (see the Supporting Information), and the best result was obtained when the reaction was conducted in DCE at room temperature (Table 1, entry 2).

Under the optimized reaction conditions, this three-component cascade process showed a broad tolerance toward various substituents on the aryl group next to the enone moiety (Table 2, entries 1–9). The process was also tolerant toward other alcohols, including bulky alcohols (Table 2, entries 10–13), and other diazo compounds (Table 2, entries 14–17). In all cases, the ability to control the formation of four new stereogenic centers enabled the synthesis of diverse 1-indanols in good yields and excellent stereoselectivity (d.r. > 20:1). The formation of multiple new stereogenic centers in one operation is still very challenging in modern organic chemistry. Although various organocatalytic methods have been reported for the formation of multiple stereogenic centers in one-pot reactions,[3e,14] this multicomponent cascade reaction represents a new strategy to build multifunctional ring systems with four contiguous stereogenic centers, including one quaternary stereocenter, in a mild, rapid, and efficient way from simple precursors.

To expand the cascade trapping process to intermolecular reactions, we conducted a four-component competitive reaction with one equivalent each of methyl phenyldiazoacetate **1a**, benzyl alcohol **2a**, benzaldehyde **5**, and chalcone **6**, and a catalytic amount of $[Rh_2(OAc)_4]$ in DCE (Scheme 3). Four-component products (**10** or **11**), which would have resulted from an intermolecular Michael-aldol-type reaction or from an aldol-aza-Michael reaction, were not formed (see the Supporting Information, Table S1). Interestingly, the product resulting from the trapping of the oxonium ylide by benzaldehyde **5** was not observed, either. Instead, the reaction just gave main product **7** from O–H insertion in 47% yield, product **8** from epoxidation of benzaldehyde in 15% yield, and product **9** from a Michael-type trapping of the oxonium

Table 1: Optimization of reaction conditions for the cascade reaction.[a]

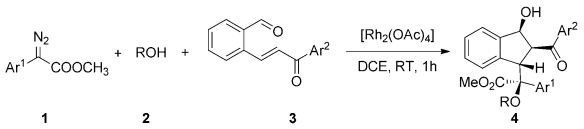


1a 2a 3a 4a

Entry	Catalyst	*T* [°C]	Yield[b] [%]	d.r.[c]
1[d]	$Cu(OTf)_2$	40	–	–
2	$[Rh_2(OAc)_4]$	RT	72	> 20:1
3[d]	$[Cu(hfaa)_2]$	RT	45	> 20:1
4[d]	$[RuCl_2(C_{10}H_{14})]$	RT	68	> 20:1

[a] Unless otherwise noted, all reactions were carried out by addition of **1a** (0.24 mmol) in DCE (1 mL) to a mixture of 2 mol% of $Rh_2(OAc)_4$, **2a** (0.24 mmol), **3a** (0.2 mmol), and 4 Å MS (0.1 g) in 2 mL of DCE under an argon atmosphere for 1 h. [b] Determined by ^1H NMR analysis. [c] Yields of isolated product **4** after purification by column chromatography. [d] Catalyst loading: 10 mol%. Bn = benzyl, DCE = 1,2-dichloroethane, hfaa = hexafluoroacetylacetone, Tf = trifluoromethanesulfonyl.

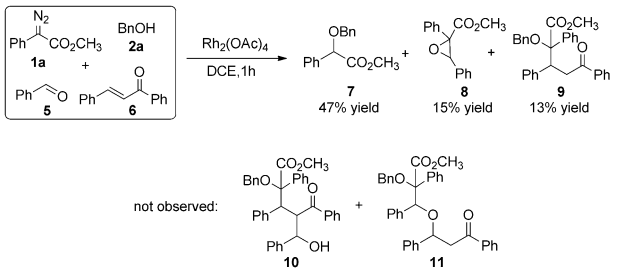
Table 2: Cascade reactions of diazo compounds with alcohols and bifunctional substrates **3**.[a]



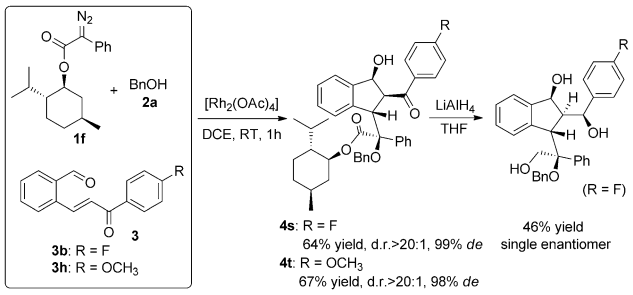
1 2 3 4

Ent.	Ar^1 (**1**)	R (**2**)	Ar^2 (**3**)	Yield[b] [%]
1	Ph (**1a**)	Bn (**2a**)	Ph (**3a**)	72 (**4a**)
2	Ph (**1a**)	Bn (**2a**)	pFC_6H_4 (**3b**)	66 (**4b**)
3	Ph (**1a**)	Bn (**2a**)	$pClC_6H_4$ (**3c**)	64 (**4c**)
4	Ph (**1a**)	Bn (**2a**)	$mClC_6H_4$ (**3d**)	75 (**4d**)
5	Ph (**1a**)	Bn (**2a**)	$oClC_6H_4$ (**3e**)	61 (**4e**)
6	Ph (**1a**)	Bn (**2a**)	$pNO_2C_6H_4$ (**3f**)	60 (**4f**)
7	Ph (**1a**)	Bn (**2a**)	$pCH_3C_6H_4$ (**3g**)	81 (**4g**)
8	Ph (**1a**)	Bn (**2a**)	$pCH_3OC_6H_4$ (**3h**)	83 (**4h**)
9	Ph (**1a**)	Bn (**2a**)	2-furyl (**3i**)	75 (**4i**)
10	Ph (**1a**)	CH_3 (**2b**)	pFC_6H_4 (**3b**)	67 (**4j**)
11	Ph (**1a**)	CH_3CH_2 (**2c**)	Ph (**3a**)	65 (**4k**)
12	Ph (**1a**)	$(CH_3)_2CH$ (**2d**)	Ph (**3a**)	70 (**4l**)
13	Ph (**1a**)	9-anthryl-CH_2 (**2e**)	Ph (**3a**)	65 (**4m**)
14	$mBrC_6H_4$ (**1b**)	Bn (**2a**)	Ph (**3a**)	61 (**4n**)
15	$pBrC_6H_4$ (**1c**)	Bn (**2a**)	Ph (**3a**)	71 (**4o**)
16	$pCH_3C_6H_4$ (**1d**)	Bn (**2a**)	Ph (**3a**)	72 (**4p**)
17	$pCH_3OC_6H_4$ (**1e**)	Bn (**2a**)	Ph (**3a**)	78 (**4q**)

For footnotes, see Table 1.



Scheme 3. Intermolecular four-component competitive reaction.

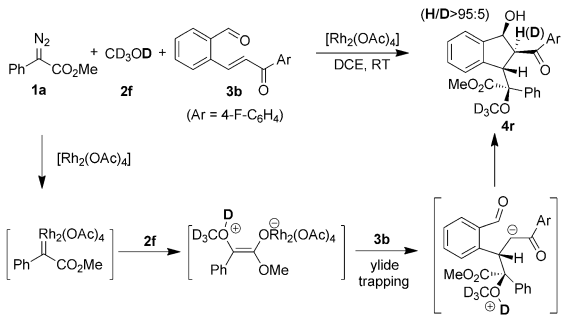


Scheme 5. . Chirality induction of oxonium ylide-trapping cascade reaction to afford 1-indanol building block bearing five stereogenic centers.

ylide in 13% yield. In addition, compared to chalcone **6**, the trapping of oxonium ylide with **3**, which contains a formyl group in *ortho* position to the enone moiety, proceeded more easily (see the Supporting Information, Table S2). All these results indicated that the formyl moiety in precursor **3** promoted the trapping of the oxonium ylide by the enone group, which is a synergistic effect between the formyl and enone groups in the trapping of active intermediates **A** and **B**.

Many reaction pathways are possible in this complex reaction system. To explore the mechanism of this cascade reaction, deuterated methanol was used for the deuterium labeling experiment to investigate the proton-transfer process (Scheme 4). Diastereomerically pure **4r**, which showed negligible deuteration (less than 5%) at the tertiary carbon center, was obtained in a good yield. This result suggests that in this system the proton transfer was successfully delayed by the additional trapping process (Scheme 2, pathway A).

Considering the great diastereoselectivity of these multicomponent cascade reactions, diazo L-menthol ester **1f** was employed as a chiral auxiliary to prepare optically active



Scheme 4. Deuterium labeling experiment for this oxonium ylide-trapping cascade reaction.

products (Scheme 5). Three-component reactions of **1f**, benzyl alcohol **2a**, and bifunctional substrate **3b** or **3h** proceed smoothly to give desired products **4s** or **4t**, respectively, in good yields with excellent diastereoselectivity. Removal of the chiral auxiliary with $LiAlH_4$ successfully gave the corresponding optically pure alcohol, which bears five stereogenic centers, in moderate yield. L-Menthol is considered one of the most convenient chiral reagents and widely employed as chiral auxiliary in asymmetric synthesis, however, examples have been limited to only moderate diastereoselectivity.[15] In the current multicomponent cascade reaction, the excellent stereoselective control may be attributed to the congested transition state, which contains all the three components, thus making chiral transfer from the auxiliary to the product very effective.

The absolute configuration of **4t** was established by X-ray single-crystal analysis and comparison with the absolute configuration of (1*R*,2*S*,5*R*)-menthol (Figure 1).

In conclusion, we have developed the first Rh^{II}-catalyzed intramolecular three-component cascade Michael-aldol-type reaction through the successive trapping of active intermediates. A delayed proton-transfer process was observed in this

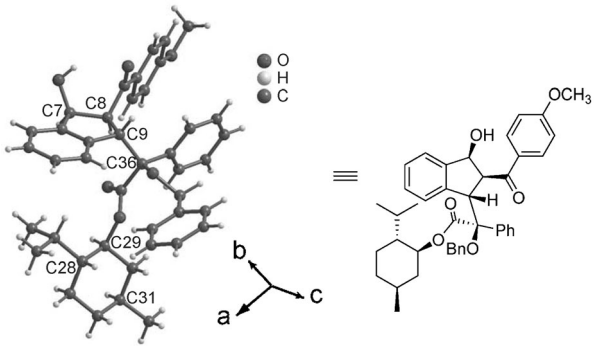


Figure 1. X-ray analysis of compound *racemic* **4t**.

novel multicomponent cascade reaction. Furthermore, a promising pathway for the introduction of chirality in this multicomponent reaction was explored and gave optically pure functionalized 1-indanol derivatives that contain multiple chiral centers with complete stereocontrol. These results gave an insight into the design of novel multicomponent cascade reactions through active trapping of intermediates for the rapid formation of complex cyclic molecules in one step.

Experimental Section

General Procedure: A flask was charged with bifunctional substrate **3** (0.20 mmol), alcohol **2** (0.24 mmol), $Rh_2(OAc)_4$ (1.0 mol%), and 4 Å molecular sieves (0.1 g) in DCE (2 mL). A solution of diazo compound **1** (0.24 mmol) in DCE (1 mL) was added to the reaction mixture over 1 h by a syringe pump. The reaction mixture was purified by flash chromatography on silica gel to give pure **4**.

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Communications

Domino Reactions

J. Jiang, X.-Y. Guan, S.-Y. Liu, B.-Y. Ren, X.-C. Ma, X. Guo, F.-P. Lv, X. Wu, W.-H. Hu* ———— ■■■■–■■■■

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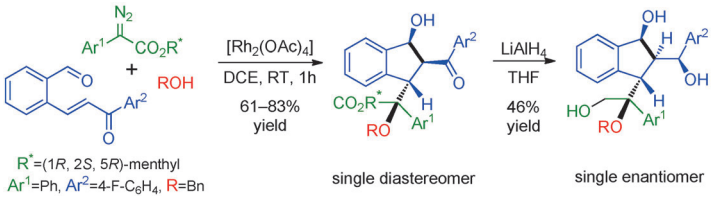

Trapped: A Michael-aldol-type cascade reaction including the trapping of an oxonium ylide through a delayed proton shift leads to the formation of multiple stereocenters in a mild one-pot synthesis. Enantiomerically pure indanol derivatives with four stereocenters and a stereogenic quaternary carbon center were easily obtained through this method in moderate to good yields.