Multicomponent Reactions

DOI: 10.1002/ange.200904905

Cooperative Catalysis in Multicomponent Reactions: Highly Enantioselective Synthesis of γ-Hydroxyketones with a Quaternary Carbon Stereocenter**

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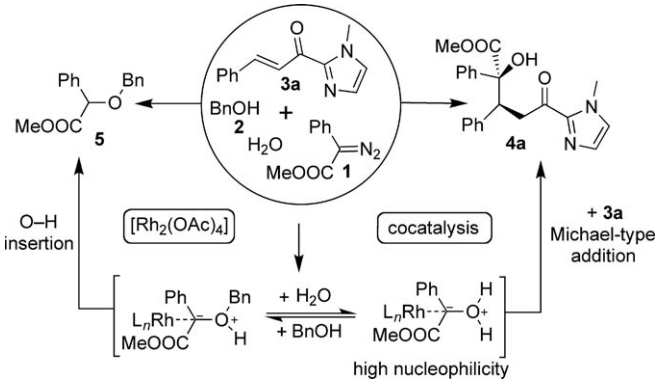
Multicomponent reactions (MCRs) offer substantial advantages over traditional approaches for the rapid generation of complex molecular architectures in a convergent and atom-economical manner.[1] Progress has recently been made with enantioselective multicomponent reactions, which enable the efficient preparation of chiral molecules from simple starting materials.[2] In recent years, cooperative catalysis, including dual-metal catalysis and metal–organo catalysis, has gained much attention in traditional two-component organic transformations owing to its ability to enhance selectivity and reactivity in the reactions.[3] In multicomponent reactions involving the formation of two or more chemical bonds, cooperative catalysis provides an opportunity to control the order of bond formation to produce different types of molecules, as the appropriate combination of compatible cocatalysts can affect the intrinsic reaction kinetics in a designed way to activate the desired component selectively.

As reactive intermediates, oxonium ylides are known to undergo synthetically useful transformations.[4] For example, transition-metal-catalyzed diastereo- and enantioselective O–H insertions of diazo compounds into alcohols or water have been studied in some detail.[5] We communicate herein that in a reaction mixture of four components—methyl phenyldiazoacetate (**1**), benzyl alcohol (**2**), water, and the conjugated enone **3a**—the traditional O–H insertion product **5** was obtained by using $[Rh_2(OAc)_4]$ alone as the catalyst, whereas the use of a cooperative catalytic system containing $[Rh_2(OAc)_4]$ as well as a Lewis acid (LA) and/or a Brønsted acid changed the reaction pathway to give the γ-hydroxyketone **4a** in good yield (Scheme 1). The trapping with a Michael acceptor of an oxonium ylide generated in situ from an aryl diazoacetate and water has not been reported previously.[6]

Our initial study began with the reaction of methyl phenyldiazoacetate (**1a**), benzyl alcohol (**2**), and the α,β-unsaturated 2-acyl imidazole **3a**. The use of $[Rh_2(OAc)_4]$ alone as the catalyst gave the O–H insertion product **5** in 65% yield (Table 1, entry 1). We envisioned that an appropriate Lewis acid cocatalyst would activate **3a**[7] through the formation of a five-membered-ring chelated intermediate. Subsequently, the oxonium ylide intermediate in the O–H insertion could be trapped by activated **3a** through a Michael-type addition to give the product of three-component coupling. To validate this hypothesis, we screened a number of Lewis acids as cocatalysts. Although $Mg(OTf)_2$, $Mg(ClO_4)_2$, and $Cu(OTf)_2$ were ineffective in the reaction, we did isolate a three-component-coupling product when we used $Zn(OTf)_2$, $Sc(OTf)_3$, or $Yb(OTf)_3$ as a cocatalyst (Table 1, entries 2–4). We were surprised to find that the obtained three-component-coupling product **4a** was derived from **1a**, **3a**, and water rather than the alcohol starting material **2**. This result indicated that incidental water in the reaction system participated in the reaction. The formation of **4a** can be accounted for by the higher nucleophilicity of the oxonium ylide formed with H_2O than that of the corresponding ylide generated with the alcohol. Among the effective cocatalysts, $Zn(OTf)_2$ gave the best result, with the formation of **4a** in 85% yield with d.r. 80:20 in favor of the *syn* isomer (Table 1, entry 4).



Scheme 1. Reaction-pathway change through cocatalysis. Bn = benzyl, L = ligand.

The above observations led us to use water (1.5 equiv) instead of benzyl alcohol in subsequent reactions. With the aim of developing an enantioselective process, we screened the chiral ligands L1–L3 in the novel three-component reaction in combination with the Lewis acid $Zn(OTf)_2$ (Table 1, entries 5–7). The complex (*S*)-*t*Bu-box–$Zn(OTf)_2$ (L1–$Zn(OTf)_2$) was the most efficient cocatalyst, with the formation of **4a** in 75% yield with d.r. 90:10 and an *ee* value of 91% for the major *syn* isomer (Table 1, entry 5). The effects of solvent and temperature on the reaction were also

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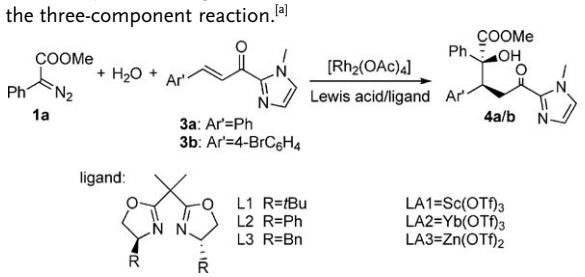
[**] We are grateful for financial support from the National Science Foundation of China (Grant No. 20932003, 20872036) and for sponsorship from Shanghai (09JC1404901, 51K03117).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200904905.

Table 1: Catalyst screening and optimization of the reaction conditions for the three-component reaction.[a]



Entry	LA (mol%)	L	3	T [°]	Yield of 4[b] [%]	d.r.[c]	ee[d] [%]
1[e]	–	–	3a	25	0[f]	n.a.	n.a
2[e]	LA1 (20)	–	3a	25	45	79:21	n.a.
3[e]	LA2 (20)	–	3a	25	80	80:20	n.a.
4[e]	LA3 (20)	–	3a	25	85	80:20	n.a.
5	LA3 (20)	L1	3a	25	75	90:10	91
6	LA3 (20)	L2	3a	25	40	83:17	29
7	LA3 (20)	L3	3a	25	70	86:14	85
8	LA3 (20)	L1	3a	−8	81	94:6	96
9[g]	LA3 (20)	L1	3a	20	86	80:20	50
10	LA3 (30)	L1	3b	−8	75	90:10	56
11[h]	LA3 (30)	L1	3b	−8	78	97:3	96

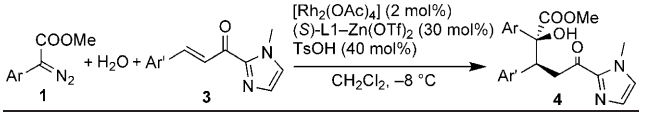
[a] Reaction conditions: **1**/H_2O/**3** = 2.5:1.5:1, [**3**] = 0.025 mmol mL^{-1} in CH_2Cl_2, inert atmosphere, 6–12 h. [b] Yield of isolated **4**. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] The *ee* value was determined by HPLC. [e] Benzyl alcohol (**2**; 0.15 mmol) was added. [f] The O–H insertion product **5** was obtained in 65% yield. [g] Excess H_2O (4 equiv) was used. [h] TsOH (40 mol%) was added. Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

investigated (see the Supporting Information). The best results were obtained when the reaction was carried out in the solvent dichloromethane at a reaction temperature of −8°C (Table 1, entry 8). The amount of water had a significant effect on the reaction. For example, when an excess amount of water (4 equiv) was used, the enantioselectivity decreased significantly to 50% *ee* (Table 1, entry 9). We next attempted to extend the optimized reaction to the bromo-substituted acyl imidazole substrate **3b**. However, the enantioselectivity of the product **4b** decreased significantly to 56% *ee* (Table 1, entry 10). We discovered that the addition of an additional Brønsted acid significantly increased the rate and selectivity of the reaction. With the addition of TsOH (40 mol%), product **4b** was obtained in 78% yield with d.r. 97:3 and 96% *ee* (Table 1, entry 11). The role of the acid additive is not yet clear, but it is likely that the Brønsted acid activates the α,β-unsaturated 2-acyl imidazole **3b** through H bonding to this substrate.

The catalyst combination $[Rh_2(OAc)_4]$, (*S*)-*t*Bu-box–Zn-$(OTf)_2$, and TsOH was applied to other acyl imidazoles **3** and aryl diazoacetates under the optimized reaction conditions (Table 2). Excellent diastereo- and enantioselectivity were consistently observed in the reaction. The configuration of the major isomer of the brominated analogue **4b** was determined to be 2*S*,3*S* by single-crystal X-ray analysis, and that of other compounds was tentatively assigned by analogy.

The 2-acyl imidazole products **4** can be transformed readily into the corresponding carboxylic acid derivatives

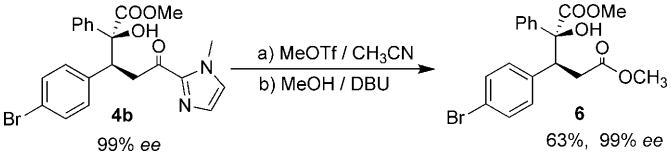
Table 2: Enantioselective three-component reaction of various diazo compounds **1** and α,β-unsaturated 2-acyl imidazoles **3** with H_2O.[a]



Entry	Ar	Ar'	Yield [%][b]	d.r.[c]	ee [%][d]
1	Ph	*p*-BrC_6H_4 (**3b**)	78 (**4b**)	97:3	96
2	Ph	*p*-ClC_6H_4 (**3c**)	75 (**4c**)	99:1	94
3	Ph	*p*-FC_6H_4 (**3d**)	70 (**4d**)	99:1	96
4	Ph	*p*-$NO_2C_6H_4$ (**3e**)	86 (**4e**)	95:5	90
5[e]	Ph	*p*-$MeOC_6H_4$ (**3f**)	60 (**4f**)	92:8	99
6[e]	Ph	*p*-MeC_6H_4 (**3g**)	63 (**4g**)	95:5	97
7	Ph	1-naphthyl (**3i**)	75 (**4i**)	86:14	95
8	Ph	*o*-ClC_6H_4 (**3k**)	61 (**4k**)	99:1	97
9	Ph	*o*-BrC_6H_4 (**3l**)	73 (**4l**)	99:1	97
10	Ph	*o*-$NO_2C_6H_4$ (**3m**)	70 (**4m**)	98:2	95
11	Ph	*o*-$OMeC_6H_4$ (**3n**)	61 (**4n**)	96:4	96
12	Ph	*m*-BrC_6H_4 (**3o**)	81 (**4o**)	99:1	96
13	Ph	*m*-$NO_2C_6H_4$ (**3p**)	61 (**4p**)	94:6	93
14	*p*-$OMeC_6H_4$	Ph (**3a**)	80 (**4j**)	99:1	93
15	*m*-ClC_6H_4	Ph (**3a**)	72 (**4q**)	99:1	85

[a] For reaction conditions, see the Supporting Information. [b] Yield of the isolated product. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] The *ee* value was determined by HPLC. [e] (*S*)-*t*Bu-box–$Zn(OTf)_2$: 50 mol%.

according to a procedure similar to a reported procedure[7b] (Scheme 2). Optically active γ-hydroxy carboxylic acid derivatives are key intermediates and building blocks in the



Scheme 2. Synthesis of the carboxylic acid derivative **6**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

synthesis of natural products and pharmaceuticals.[8] Significant efforts have already been made in the preparation of chiral γ-hydroxy carboxylic acid derivatives;[9] we now add an efficient method for the construction of such a framework with contiguous quaternary and trisubstituted stereogenic carbon centers.[10]

In summary, we have developed an enantioselective three-component reaction of diazo compounds with H_2O and α,β-unsaturated 2-acyl imidazoles in the presence of $[Rh_2(OAc)_4]$, (*S*)-*t*Bu-box–$Zn(OTf)_2$, and TsOH. The reaction provides an efficient route to γ-hydroxyketone derivatives containing a stereogenic quaternary carbon center in good yield with excellent enantioselectivity. We anticipate that the concept of cooperative catalysis will be applicable to the discovery of more novel multicomponent reactions.

Experimental Section

Typical procedure: CH_2Cl_2 was distilled over calcium hydride until a water content of 0.05% (w/w) in the solvent was reached. The water

serves as a reactant in the multicomponent reaction, and the amount of water is critical for the success of the reaction. Zinc(II) triflate (10.8 mg, 0.03 mmol) and (*S*)-*t*Bu-box (10.5 mg, 0.036 mmol) were placed in a flame-dried vial, which was then capped with a septum. CH_2Cl_2 (1 mL) was added, and the mixture was stirred for 1 h at 25 °C. A solution of 3-(4-bromophenyl)-1-(1-methyl-1*H*-imidazol-2-yl)prop-2-en-1-one (**3b**; 0.1 mmol), $[Rh_2(OAc)_4]$ (1 mg, 0.0022 mmol), and 4-toluenesulfonic acid (8 mg, 0.042 mmol) in CH_2Cl_2 (2 mL) was then added, and the resulting mixture was stirred for 5 min at room temperature, then cooled to −8 °C and stirred for 10 min at this temperature. Methyl phenyldiazoacetate (**1a**; 44 mg, 0.25 mmol) in CH_2Cl_2 (1 mL) was then added, and the reaction mixture was stirred for 6–12 h at −8 °C until completion of the reaction was indicated by TLC. The reaction mixture was concentrated under reduced pressure, and the diastereomeric ratio of the crude product was determined by ^{1}H NMR spectroscopic analysis. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/light petroleum 1:3) to give **4b** (35.6 mg, 78 %). The optical purity of the product was determined by HPLC analysis on a chiral phase (Daicel Chiralpak AD-H column).

Received: September 2, 2009
Published online: November 5, 2009

Keywords: asymmetric synthesis · cooperative catalysis · Michael addition · multicomponent reactions · oxonium ylides

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