Multicomponent Reactions

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Catalytic Enantioselective Trapping of an Alcoholic Oxonium Ylide with Aldehydes: Rh^{II}/Zr^{IV}-Co-Catalyzed Three-Component Reactions of Aryl Diazoacetates, Benzyl Alcohol, and Aldehydes**

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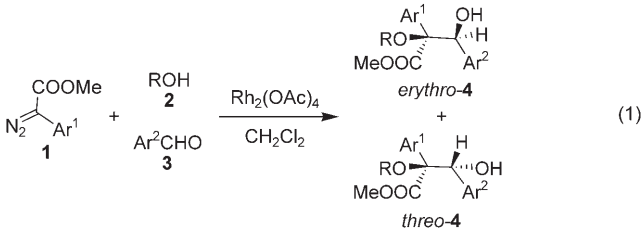
Catalytic asymmetric multicomponent reactions (CAMCRs), in which three or more reactants are combined in a single chemical step to stereoselectively produce chiral molecules, have received considerable attention.[1] In addition to lowering costs, saving time and energy, and being environmentally friendly, CAMCRs are capable of efficiently building chiral molecules such as those with stereogenic quaternary carbon atoms that would otherwise be inaccessible by traditional methods.[2] Although significant progress has been made in the area of multicomponent reactions,[1d,3] there is still a high demand for new CAMCRs to meet the increasing need for the rapid construction of polyfunctional chiral molecules. Herein we disclose a novel type of CAMCR in which polyfunctional dihydroxy acid derivatives with two stereogenic centers, one of which is a tetrasubstituted carbon center, are constructed in a single step.

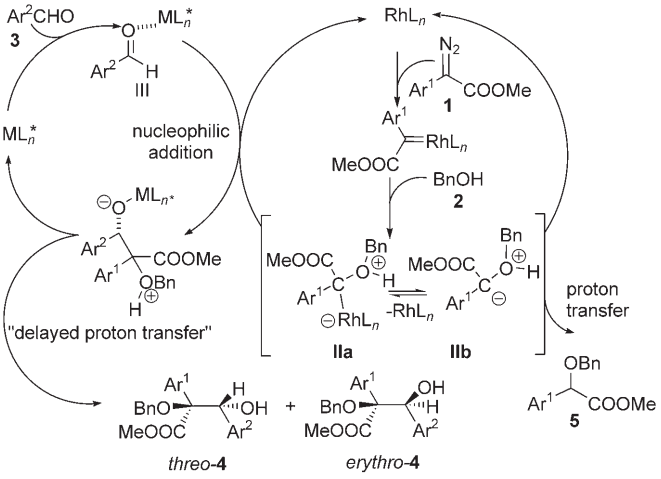
We have previously reported three-component reactions of diazo compounds **1**, alcohols **2**, and aldehydes **3** to yield racemic mixtures of dihydroxy acid frameworks with quaternary stereogenic centers **4** [Eq. (1)].[4c] The reaction was proposed to proceed through the alcoholic oxonium ylide intermediates **IIa** or **IIb** (Scheme 1), which are generated in situ from **1** and benzyl alcohol (**2**) in the presence of $Rh_2(OAc)_4$. Trapping intermediates **II** with aldehydes resulted in **4**; the desired process was in competition with an irreversible intramolecular proton transfer within **IIa/IIb** leading to the O–H insertion side products **5** (Scheme 1). We also observed that addition of a stoichiometric amount of the Lewis acid $Ti(OtBu)_4$ suppressed the O–H insertion.[4c] This observation supported the proposed mechanism, including the competing intramolecular process, because the Lewis acid would have increased the electrophilicity of the aldehydes,



(1)

and thereby activating them. On the basis of this observation and the previous success of chiral Lewis acid catalysts in facilitating highly enantioselective aldol reactions,[5] we envisioned that by using appropriate chiral Lewis acid co-catalysts it might be possible to achieve asymmetric catalysis of the target three-component reaction. In the presumed mechanism, an alcoholic oxonium ylide **II**, which is formed in situ from a diazoacetate and an alcohol, would experience a "delayed proton transfer" and instead undergo an enantioselective aldol-type addition onto an aldehyde **III** activated with chiral Lewis acid to generate optically active **4** (Scheme 1).

To validate the hypothesis a number of chiral Lewis acids,[5] such as combinations of $Cu(OTf)_2$, $Yb(OTf)_3$, $Mg(ClO_4)_2$, or $Sn(OTf)_2$ (Tf = trifluoromethanesulfonyl) with chiral bisoxazoline ligands and combinations of Ti^{IV} salts with chiral binol (binol = (1,1′-bi-2-naphthyl)) derivatives, were screened as chiral co-catalysts for the target CAMCR. None yielded satisfactory chemo- and stereoselectivities. Never-



Scheme 1. Proposed mechanism for the target CAMCR. ML_n* = chiral Lewis acid, Bn = benzyl.

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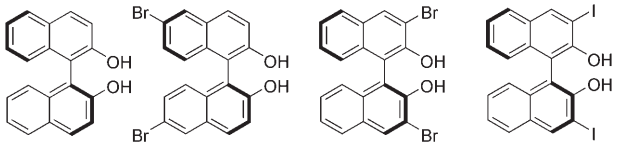
theless, the zirconium–binol system developed by Kobayashi and co-workers[6] was identified as the best co-catalysts for generating the desired optically active products.

The Kobayashi research group has developed air-stable, chiral Zr/binol/molecular sieves catalysts by combining Zr(O*n*Bu)$_4$, chiral binol ligands **6**, and 5 Å molecular sieves (M.S.) in appropriate quantities.[6b,c] We found that these catalysts effectively catalyzed the target three-component reactions. In the absence of a Zr/binol/M.S. co-catalyst, $Rh_2(OAc)_4$ catalyzed the reaction of methyl phenyldiazoacetate (**1a**) with benzaldehyde and benzyl alcohol to generate only the O–H insertion product **5** (Table 1 entry 1). In

Table 1: Effect of chiral ligands on Zr(O*n*Bu)$_4$/**6**/M.S.-catalyzed aldol-type reactions of benzaldehyde and BnOH with methyl phenyl diazoacetate.



Entry	Ligand (mol%)	*T* [°C]	Solvent	Yield [%][b]	d.r.[c] (*erythro*-**4a**/*threo*-**4a**)	*ee* [%][d]
1	–	25	CH_2Cl_2	–	–	–
2	**6a** (15)	25	CH_2Cl_2	10	85:15	10
3	**6b** (15)	25	CH_2Cl_2	30	60:40	15
4	**6c** (15)	25	CH_2Cl_2	39	85:15	80
5	**6d** (5)	25	CH_2Cl_2	30	62:38	54
6	**6d** (15)	25	CH_2Cl_2	43	80:20	90
7	**6d** (30)	25	CH_2Cl_2	54	91:9	94
8	**6d** (15)	25	toluene	54	84:16	91
9	**6d** (15)	0	DCE	81	90:10	98
10	**6d** (15)	0	toluene	73	87:13	96
11	**6d** (15)	−20	DCE	87	87:13	93
12	**6d** (15)	−20	toluene	78	88:12	94

[a] Reactions were performed on a 0.1 mmol scale (**1a**/**2**/**3a** 1:1.2:1.1) in the presence of $Rh_2(OAc)_4$ (1 mol%) in solvent (3.0 mL) at the given temperature in an Ar atmosphere. [b] Yield of isolated product after purification by column chromatography. [c] Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. [d] The *ee* values were determined by HPLC on a chiral stationary phase.

contrast, the addition of 15 mol% Zr/(*S*)-**6a**/M.S.[6d] resulted in the isolation of the desired diastereomers (*erythro*-**4a** and *threo*-**4a**) in 10% yield, with 10% *ee* for the favored *erythro* diastereomer (Table 1 entry 2). This result encouraged us to screen other binol ligands, and of those (*S*)-3,3′-diiodobinol **6d** gave the most promising results: products **4a** were isolated in 43% yield (*erythro*-**4a**/*threo*-**4a** 80:20) with 90% *ee* for the major diastereomer (Table 1 entry 6). A higher yield of *erythro*-**4a** with 94% *ee* was obtained when the catalyst loading was increased to 30 mol% (Table 1, entry 7). The effects of solvent and temperature were also investigated (Table 1, entries 8–13), and the optimized reaction conditions involved 1,2-dichloroethane (DCE) at 0 °C in the presence of 15 mol% Zr/**6d**/M.S. co-catalyst (Table 1, entry 9), which generated the desired products in 81% overall yield (*erythro*-**4a**/*threo*-**4a** 90:10) with 98% *ee* for *erythro*-**4a**.

The scope and limitations of the optimized reaction conditions were investigated and were found to be amenable to the reaction of benzyl alcohol with other aldehydes and diazo compounds (Table 2). Various aryl aldehydes with

Table 2: Catalytic asymmetric aldol-type reactions of aryl diazoacetates with BnOH and aldehydes using the Zr(O*n*Bu)$_4$/**6d**/M.S. co-catalyst.

Entry	Ar^1	Ar^2	Yield **4** [%][b]	d.r. (*erythro*/*threo*)[c]	*ee* [%][d]
1	Ph	Ph	81 (**4a**)	90:10	98
2	Ph	*p*-MeOPh	68 (**4b**)	80:20	96
3	Ph	*p*-BrPh	80 (**4c**)	89:11	94
4	Ph	*p*-ClPh	77 (**4d**)	90:10	95
5	Ph	*p*-NO_2Ph	43 (**4e**)	70:30	60
6	Ph	3,4-(OCH_2O)Ph	82 (**4f**)	83:17	96
7[e]	Ph	1-naphthyl	40 (**4g**)	90:10	78
8	Ph	cinnamonyl	78 (**4h**)	84:16	94
9	Ph	2-furyl	72 (**4i**)	91:9	92
10	*p*-BrPh	Ph	70 (**4j**)	92:8	96
11	*p*-BrPh	*p*-MeOPh	73 (**4k**)	93:7	93
12	*m*-MePh	Ph	60 (**4l**)	89:12	96
13	*m*-MePh	*p*-MeOPh	65 (**4m**)	90:10	97
14	*m*-MePh	*p*-BrPh	66 (**4n**)	82:18	89

[a] Reactions performed in DCE at 0 °C in the presence of $Rh_2(OAc)_4$ (1 mol%) and Zr/**6d**/M.S. (15 mol%). [b] Yield of isolated product after purification by column chromatography. [c] Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. [d] The *ee* values were determined by HPLC on a chiral stationary phase. [e] Zr(O*n*Bu)$_4$/**6d** 1.0:1.2.

different substituents were found to be good substrates. Reactions with cinnamaldehyde and furfural aldehyde afforded the corresponding products **4h** and **4i**, respectively, in moderate yields and high diastereo- and enantioselectivities (Table 2, entries 8 and 9). The reaction was observed to be somewhat sensitive to electronic effects: the reaction of an electron-withdrawing substrate, *p*-nitrobenzaldehyde, gave a lower yield and only moderate enantioselectivity (Table 2, entry 5). The reaction did not work well with aliphatic aldehydes, and the use of ethyl diazoacetate failed to produce the desired product. The absolute configuration of the major *erythro*-**4a** enantiomer was assigned as 2*S*,3*S* by comparison with published data for the corresponding debenzylated compound (2*S*,3*S*)-methyl 2,3-dihydroxy-2,3-diphenylpropanoate.[7]

The enantioselective oxonium-trapping process reported herein is quite unique. The alcoholic oxonium ylide intermediates **IIa** and **IIb** are unstable and possess extremely short half-lives which undergo fast, irreversible proton transfer that results in the formation of the undesired O–H insertion side product.[8] By employing an appropriate chiral Lewis acid co-catalyst, we were not only able to control the reaction pathway by efficiently trapping the oxonium ylide to form the desired product, we were also able to achieve high diastereoselectivities and excellent enantioselectivities.

In conclusion, we have developed Rh^{II}/Zr^{IV}-co-catalyzed asymmetric three-component reactions that combine aryl

diazoacetates, benzyl alcohols, and aldehydes. The reaction occurs by trapping a reactive alcoholic oxonium ylide with a Zr^{IV}-activated aldehyde. The reaction provides a convenient and highly enantioselective route to the construction of an important class of compounds for both organic and medicinal chemistry; namely, α,β-dihydroxy acid derivatives containing chiral tetrasubstituted carbon centers.

Experimental Section

Typical experimental procedure for asymmetric aldol-type reactions with a chiral zirconium catalyst: BnOH (12.5 μL, 0.12 mmol) was added to a mixture of powdered Zr catalyst[6d] (0.015 mmol) in DCE (1.00 mL) at room temperature. The mixture was stirred for 1 h before a solution of benzadehyde (0.11 mmol) and $Rh_2(OAc)_4$ (0.5 mg, 1 mol%) in DCE (0.50 mL) was added. The resulting mixture was stirred at room temperature for 5 min and then cooled to 0°C for 10 min before methyl phenyldiazoacetate (**1a**; 17.6 mg, 0.10 mmol) in DCE (1 mL) was added. The reaction mixture was stirred for 3–4 h at 0°C until the reaction was complete (as evident by TLC) and was subsequently quenched by the addition of a saturated aqueous solution of $NaHCO_3$. After removal of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2×10 mL) and the organic extracts were then combined, dried over anhydrous Na_2SO_4, and the filtrate was concentrated under reduced pressure to give the crude product. ^1H NMR analysis was used to determine the diastereoselectivity of the reaction. The crude product was then purified by flash chromatography on silica gel (EtOAc/light petroleum 1:15) to yield **4a** (29.3 mg, 81%). The optical purity was determined by HPLC on a chiral stationary phase using a Daicel Chirapak OD-H column. Compounds **4b**–**4n** were prepared by similar procedures.

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