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Copper(II)-catalyzed highly diastereoselective three-component reactions of aryl diazoacetates with alcohols and chalcones: an easy access to furan derivatives†

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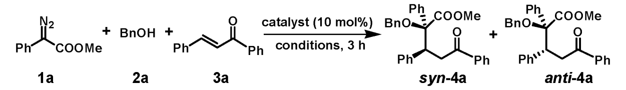
Copper(II) complexes are efficient catalysts in three-component reactions of aryl diazoacetates with alcohols and chalcones to give γ-hydroxyketone derivatives in high yield with excellent diastereoselectivity. The resulting coupling adducts can be easily converted into furan-containing oligoaryls, tetrahydrofuran and 2,3-dihydrofuran derivatives.

Development of highly efficient synthetic strategies for rapid construction of complex molecular architectures is of growing interest and remains a great challenge in modern synthetic organic chemistry.[1] Compared to traditional chemical reactions, multi-component reactions[2] (MCRs) make it possible to accomplish these goals due to their high synthetic efficiency, atom economy, flexibility and simplicity.

Ylide chemistry is an area of continuing interest.[3] We have discovered a novel oxonium ylide chemistry that alcoholic oxonium ylides generated *in situ* from diazo compounds and alcohols in the presence of $Rh_2(OAc)_4$ can be trapped by aldehydes and imines.[4] Most recently, the efficient trapping process was extended to α,β-unsaturated 2-acyl imidazoles by applying a co-catalysis strategy.[5] However, expensive $Rh_2(OAc)_4$ catalyst has to be employed in most cases in the reactions.[6] Copper catalysts are highly attractive for chemical synthesis from environmental and economic points of view,[7] and copper complexes have shown different properties in transition-metal catalyzed diazo decomposition reactions including cyclopropanation,[8a–d] aziridination,[8e,f] O–H insertion,[8g,h] N–H insertion.[8i,j] Herein, we report that copper complexes are superior catalysts than $Rh_2(OAc)_4$ in the stereoselective three-component reactions of aryl diazoacetates, alcohols and chalcones. Thus, γ-hydroxyketone derivatives can be efficiently constructed. Notably, the three-component reaction can be scaled up to multigram scale by using $CuSO_4$ as the catalyst.

Table 1 Catalyst screening and optimization of reaction conditions[a]



Entry	Catalyst	Solvent	T/°C	Yield[b] (%)	Dr[c] (*syn* : *anti*)
1[d]	$Rh_2(OAc)_4$	CH_2Cl_2	rt	19	>95 : 5
2[e]	$Rh_2(OAc)_4$	CH_2Cl_2	rt	37	>95 : 5
3	$Cu(CH_3CN)_4PF_6$	CH_2Cl_2	rt	71	>95 : 5
4	CuOTf	CH_2Cl_2	rt	69	>95 : 5
5	$Cu(OTf)_2$	CH_2Cl_2	rt	84	>95 : 5
6	$Cu(acac)_2$	CH_2Cl_2	rt	39	>95 : 5
7[f]	$CuSO_4$	CH_2Cl_2	rt	80	>95 : 5
8	$Cu(OTf)_2$	$CHCl_3$	rt	78	94 : 6
9	$Cu(OTf)_2$	$ClCH_2CH_2Cl$	rt	72	92 : 8
10	**$Cu(OTf)_2$**	**CH_2Cl_2**	**40**	**88**	**>95 : 5**
11	$Cu(OTf)_2$	CH_2Cl_2	0	69	>95 : 5

[a] Unless otherwise noted, the reaction was carried out on 0.2 mmol scale, and to a mixture of **2a** (0.24 mmol), **3a** (0.2 mmol) , catalyst and solvent (2 mL) was slowly added **1a** (0.24 mmol) in the corresponding solvent (1 mL) over 3 h *via* a syringe pump. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] 2 mol% of catalyst loading. [e] 10 mol% of $Zn(OTf)_2$ was added. [f] 20 mol% of catalyst loading.

In continuation of our research interest by using an enone to trap an alcoholic oxonium ylide,[5] we first examined the reaction of methyl phenyl diazoacetate (**1a**), benzyl alcohol (**2a**) and chalcone (**3a**) in the presence of $Rh_2(OAc)_4$. The desired Michael addition trapping product was obtained in a very low yield (19%). Significant amount of O–H insertion side product was observed (Table 1, entry 1). To enhance the product yield, Lewis acids such as $Zn(OTf)_2$, which was demonstrated as an effective co-catalyst,[5] were employed to activate the enone substrate. The product yield was increased slightly to 37% (entry 2). To our delight, the yield was sharply increased to 71% when $CuPF_6(CH_3CN)_4$ was used as a catalyst (entry 3). Encouraged by the result, a number of copper complexes including Cu(II) were screened (Table 1, entries 3–7). Among the copper catalysts tested, $Cu(OTf)_2$ was the best giving the highest yield of 84% with >95 : 5 diastereoselectivity, favoring the *syn* diastereomer (Table 1, entry 5). Other solvents such as $CHCl_3$ and $ClCH_2CH_2Cl$ were used, and slightly lower product yields and decreased diastereoselectivity were observed in comparison with CH_2Cl_2 (Table 1, entries 8 and 9 *vs.* entry 5). The effect of reaction temperature on the yield was also investigated. The highest yield of 88% was obtained when the reaction was carried out at 40 °C without compromising of the diastereoselectivity (>95 : 5) (Table 1, entry 10).

With the optimized reaction conditions in hand, we then proceeded to investigate the reaction scope. As shown in Table 2, the present three-component reaction was well tolerated to electronic properties of the substrates. Good to

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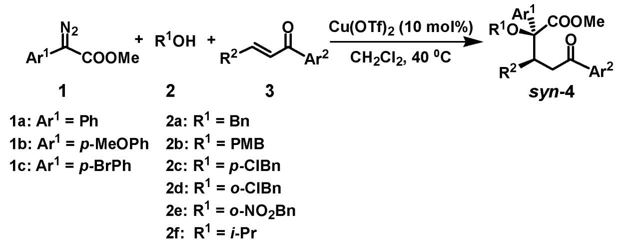
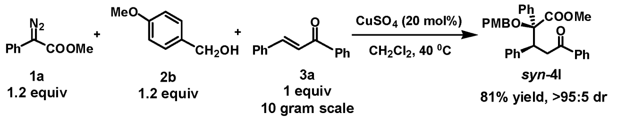
Table 2 Michael addition three-component reaction of aryl diazoacetates with alcohols and enones[a]

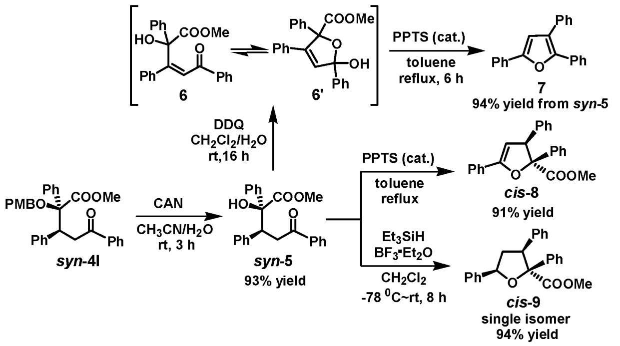


Entry	1	2	R^2, Ar^2 (3)	Product	Yield[b] (%)	Dr[c] (*syn* : *anti*)
1	**1a**	**2a**	Ph, Ph (**3a**)	**4a**	88	>95 : 5
2	**1a**	**2a**	*p*-ClPh, Ph (**3b**)	**4b**	85	>95 : 5
3	**1a**	**2a**	*o*-ClPh, Ph (**3c**)	**4c**	83	>95 : 5
4	**1a**	**2a**	*p*-BrPh, Ph (**3d**)	**4d**	86	>95 : 5
5	**1a**	**2a**	*o*-BrPh, Ph (**3e**)	**4e**	89	>95 : 5
6	**1a**	**2a**	*m*-BrPh, Ph (**3f**)	**4f**	82	>95 : 5
7	**1a**	**2a**	*p*-MeOPh, Ph (**3g**)	**4g**	93	>95 : 5
8	**1a**	**2a**	Ph, *p*-ClPh (**3h**)	**4h**	92	>95 : 5
9	**1a**	**2a**	Ph, *p*-MeOPh (**3i**)	**4i**	86	>95 : 5
10	**1a**	**2a**	2-Thienyl, Ph (**3j**)	**4j**	81	>95 : 5
11	**1c**	**2a**	Me, *p*-MeOPh (**3k**)	**4k**	63	90 : 10
12	**1a**	**2b**	Ph, Ph (**3a**)	**4l**	94	>95 : 5
13	**1a**	**2c**	Ph, Ph (**3a**)	**4m**	86	>95 : 5
14	**1a**	**2d**	Ph, Ph (**3a**)	**4n**	88	>95 : 5
15	**1a**	**2e**	Ph, Ph (**3a**)	**4o**	81	>95 : 5
16	**1a**	**2f**	Ph, Ph (**3a**)	**4p**	78	>95 : 5
17	**1b**	**2a**	Ph, Ph (**3a**)	**4q**	92	>95 : 5
18	**1c**	**2a**	Ph, Ph (**3a**)	**4r**	83	>95 : 5

[a] Unless otherwise noted, the reaction was carried out with **1** (0.36 mmol), **2** (0.36 mmol) and **3** (0.3 mmol) in the presence of $Cu(OTf)_2$ (10 mol%) in CH_2Cl_2 at 40 °C for 3 h. [b] Isolated yield. [c] Determined by ^1H NMR of the crude reaction mixture.



Scheme 1 Scale-up of the Michael-type three-component reaction.



Scheme 2 Synthetic application of the Michael adduct.

excellent yields (81–94%) were obtained with substrates bearing either electron-withdrawing or donating groups on the aryl rings of chalcones (Table 2, entries 2–9), benzyl alcohols (entries 12–15) and aryl diazoacetates (entries 17 and 18). Good yield and excellent stereoselectivity were also observed in the reaction with a chalcone bearing heteroaromatic substituent (entry 10). The use of the enone substrate **3k** bearing an alkyl substituent on the C=C bond also gave the desired product, but with slightly lower yield (63%) and decreased diastereoselectivity (90 : 10) (Table 2, entry 11). Other alcohols such as isopropyl alcohol (**2f**) was also a suitable substrate to give the corresponding product **4p** in 78% yield (Table 2, entry 16).

The relative stereochemistry of the product was established by single-crystal X-ray analysis of *syn*-**4r** (see ESI‡).

The present three-component reaction can be scaled up to a multigram scale as exemplified in Scheme 1. In this case, we used the cheapest copper salt, $CuSO_4$, as a catalyst. Thus, the three-component reaction of chalcone **3a** (10 g, 1 equiv.) with methyl phenyl diazoacetate **1a** (1.2 equiv.) and *p*-methoxybenzyl alcohol **2b** (1.2 equiv.) afforded the product *syn*-**4l** in 81% yield with excellent diastereoselectivity (*syn* : *anti* > 95 : 5).

Furan-containing oligoaryls have been reported to exhibit promising characteristics as hole transporting materials for organic light-emitting diodes (OLEDs),[9] and many efforts have been made for the efficient preparation of oligoaryl compounds.[9a,e,10] The synthetic utility of the current method was demonstrated in a facile access to the furan-containing oligoaryls (Scheme 2). For example, deprotection of *syn*-**4l** with cerium(IV) ammonium nitrate (CAN) in wet CH_3CN gave γ-hydroxyketone *syn*-**5** in 93% yield. Oxidation of *syn*-**5** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) followed by treatment with a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) afforded 2,3,5-triphenylfuran (**7**) in 94% overall yield.‡ This should represent a novel and convenient approach to furan-containing oligoaryls. In direct treatment of *syn*-**5** with PPTS (20 mol%), polysubstituted 2,3-dihydrofuran *cis*-**8** was obtained in 91% yield.[11] Alternatively, *syn*-**5** can be converted into polysubstituted tetrahydrofuran *cis*-**9** as a single diastereomer under reducing conditions by using $Et_3SiH/BF_3{\cdot}Et_2O$.[12] The relative stereochemistry of *cis*-**9** was confirmed by single-crystal X-ray structure analysis‡ to show the all *cis*-relationship of the three phenyl substituents (see ESI†). Polysubstituted furan,[13] tetrahydrofuran[14] and dihydrofuran[15] moieties are frequently found in numerous biologically active natural products and pharmaceutical agents.

In summary, we have developed a novel three-component reaction of an aryl diazoacetate, an alcohol and chalcone. Copper complexes were found to be effective and efficient catalysts in the reaction. The Michael-type reaction performed well over a broad range of substrates to give the desired products in high yields (up to 94%) with excellent diastereoselectivity (>95 : 5). The present synthetic approach can also be scaled up to a multigram scale and the product can be readily converted into furan-containing oligoaryls, polysubstituted tetrahydrofuran and 2,3-dihydrofuran derivatives.

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Notes and references

‡ *Crystal data* for *syn*-**4r**: $C_{31}H_{27}BrO_4$, $M = 543.44$, monoclinic, space group $P2_1/c$, 0.48 × 0.26 × 0.22 mm, $a = 11.0837(4)$, $b = 12.5162(4)$, $c = 19.9846(7)$ Å, $\beta = 105.7030(10)$, $V = 2668.91(16)$ Å^3, $Z = 4$,

D_c = 1.352 Mg m^{-3}, T = 296(2) K, 30 268 reflections collected, 4691 unique (R_{int} = 0.0283). Final R indices R_1 = 0.0471 with $I > 2\sigma(I)$, wR_2 = 0.1251 for all data.

Crystal data for **7**: $C_{22}H_{16}O$, M = 296.35, orthorhombic, space group $Pbca$, 0.52 × 0.48 × 0.36 mm, a = 7.7124(4), b = 19.8082(9), c = 20.3303(10) Å, V = 3105.8(3) Å^3, Z = 8, D_c = 1.268 Mg m^{-3}, T = 173(2) K, 32 737 reflections collected, 2731 unique (R_{int} = 0.0247). Final R indices R_1 = 0.0501 with $I > 2\sigma(I)$, wR_2 = 0.1334 for all data.

Crystal data for *cis*-**9**: $C_{24}H_{22}O_3$, M = 358.42, orthorhombic, space group $P2_12_12_1$, 0.52 × 0.44 × 0.32 mm, a = 8.6978(3), b = 9.0256(3), c = 23.8222(9) Å, V = 1870.11(11) Å^3, Z = 4, D_c = 1.273 Mg m^{-3}, T = 173(2) K, 21 736 reflections collected, 1903 unique (R_{int} = 0.0862). Final R indices R_1 = 0.0293 with $I > 2\sigma(I)$, wR_2 = 0.0742 for all data.

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