Asymmetric Synthesis

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Asymmetric Synthesis of Dihydropyranones from Ynones by Sequential Copper(I)-Catalyzed Direct Aldol and Silver(I)-Catalyzed Oxy-Michael Reactions**

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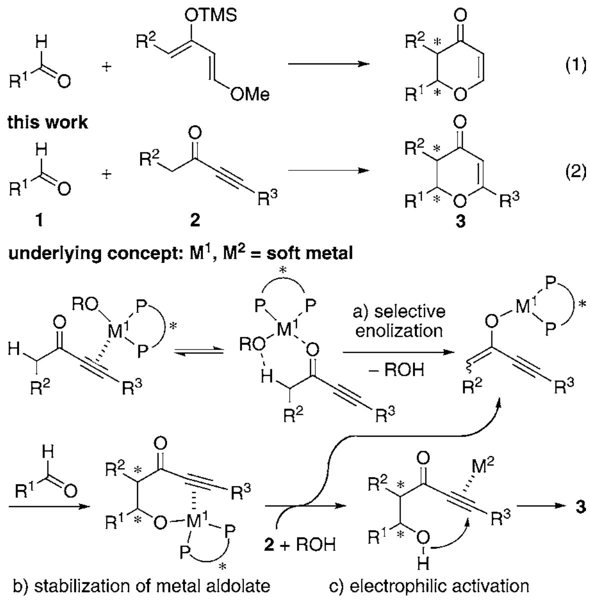
Chiral dihydropyranones are versatile intermediates for the synthesis of tetrahydropyrans and spiroketals, which are ubiquitous structural motifs in biologically active molecules. The asymmetric hetero-Diels–Alder reaction[1] between carbonyl compounds and Danishefsky-type siloxy dienes is one of the most reliable methods of accessing optically active dihydropyranones [Scheme 1, Eq. (1)]. However, this method requires additional steps for the preparation of siloxy dienes, and the stereoselective synthesis of multisubstituted siloxy dienes is generally difficult. Considering the fact that enolates derived from ynones **2**[2] are in the same oxidation state as Danishefsky-type dienes, we envisioned that a stepwise catalytic asymmetric direct aldol reaction of ynones, followed by an intramolecular oxy-Michael reaction would produce enantiomerically enriched dihydropyranones [Scheme 1, Eq. (2)]. This sequential pathway would be atom-economical[3] and require fewer steps.[4] Herein, we report the catalytic asymmetric synthesis of 2,6-disubstituted and 2,3,6-trisubstituted dihydropyranones by a sequential aldol-oxy-Michael reaction using stable and easily accessible ynones.

Despite the high synthetic utility of the products, to date there have been only three reports of direct catalytic enantioselective aldol reactions[5] between aldehydes and ynones.[6,7] However, the substrate scope of these previous examples is not satisfactory, being limited to either unenolizable α,α-disubstituted aliphatic aldehydes[6a–d] or aromatic aldehydes with strong electron-withdrawing groups.[6e] In addition, intramolecular oxy-Michael reactions of ynones producing dihydropyranones have not been studied extensively.[8,9] The high susceptibility of aldol intermediates derived from ynones to the retro-aldol reaction is the most common reason for this lack of research into the use of ynones in aldol and oxy-Michael reactions. To enhance the feasibility of sequential dihydropyranone synthesis, potential catalysts should promote the aldol and oxy-Michael steps under very mild conditions.



Scheme 1. Two methods for the catalytic asymmetric synthesis of dihydropyranones. TMS = trimethylsilyl.

We envisioned that soft metal catalysts, which preferentially interact with the C≡C bond moiety of ynones, would effectively suppress the undesired retro-aldol reaction in this sequential process (Scheme 1). There are three main advantages to using soft metal catalysts in this process. First, the interaction of these catalysts with the substrate facilitates the selective deprotonation of ynones, even in the presence of enolizable aliphatic aldehydes under weakly basic conditions.[10] Second, the intermediate soft metal aldolate is stabilized due to the additional metal–π interaction, allowing for retardation of the undesired retro-aldol reaction. Third, the interaction activates the C≡C bond, and facilitates the intramolecular oxy-Michael reaction under non-basic conditions. M^1 and M^2 can either be the same metal (preferably) or different metals.

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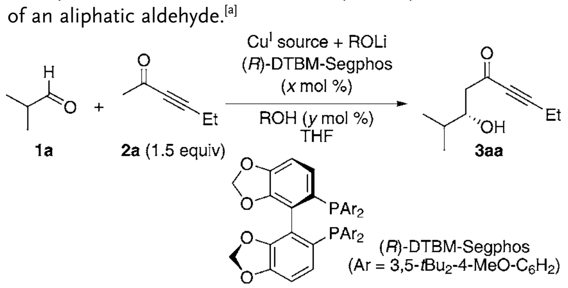
Based on our previous findings,[10b–e] we began by examining the asymmetric aldol addition of 3-hexyn-2-one (**2a**) and isobutyraldehyde (**1a**) using copper alkoxide- or phenoxide-phosphine complexes ($M^1 = Cu$, Table 1) as catalysts. Initial ligand screening[11] indicated that a catalyst derived from $CuPF_6$, $Li(OC_6H_4\text{-}p\text{-}OMe)$, and (*R*)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole (DTBM-Segphos) at −20 °C gave promising results, affording β-hydroxyynones **3aa** in 84 % yield and 30 % *ee* (Table 1, entry 1). The subsequent oxy-Michael reaction did not proceed under those conditions. Therefore, we first optimized the direct catalytic asymmetric aldol reaction. Notably, either lowering the temperature to −30 °C (Table 1, entry 2) or using an additional 15 mol % of $p\text{-MeO-}C_6H_4OH$ (pK_a in DMSO = 19.1, Table 1, entry 3) significantly improved the enantioselectivity to greater than 80 %, although the yield of **3aa** was moderate. The effects of the copper source were minor, although the use of $CuClO_4$ instead of $CuPF_6$ slightly improved the yield without changing the enantioselectivity (Table 1, entry 4).

Table 1: Optimization of Cu^I alkoxide-catalyzed asymmetric aldol reaction of an aliphatic aldehyde.[a]



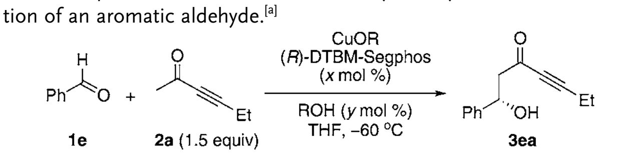
Entry	Cu source (*x*)[b]	R	*y*	Yield [%][c]	*ee* [%]
1[d]	$CuPF_6$ (10)	$p\text{-MeO-}C_6H_4$	0	84	30
2	$CuPF_6$ (10)	$p\text{-MeO-}C_6H_4$	0	69	81
3	$CuPF_6$ (10)	$p\text{-MeO-}C_6H_4$	15	65	88
4	$CuClO_4$ (10)	$p\text{-MeO-}C_6H_4$	15	76	88
5	$CuClO_4$ (10)	CF_3CH_2	15	86	33
6	$CuClO_4$ (10)	CF_3CH_2	200	100	81
7[e]	$CuClO_4$ (3)	CF_3CH_2	40	96	88
8[f]	$CuClO_4$ (5)	$(CF_3)_2CH$	5	91	89

[a] Reactions conducted at −30 °C for 13 h, unless otherwise noted. [b] Tetraacetonitrile complexes were used. [c] Determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [d] At −20 °C. [e] At −40 °C for 20 h. [f] For 36 h.

To improve the yield further, we used a more basic catalyst containing trifluoroethoxide (pK_a of trifluoroethanol (TFE) in DMSO = 23.5). As expected, the yield was higher (86 %), but the enantiomeric excess dropped to 33 % (Table 1, entry 5). This dramatic decrease in enantioselectivity when using a catalyst with higher basicity is likely due to the basic conditions facilitating the retro-aldol reaction through a metal aldolate intermediate.[6c] Excess alcohol was added to prevent the retro-aldol reaction by decreasing the concentration of metal aldolate (Table 1, entry 6). A marked improvement in enantioselectivity to 81 % was observed. Finally, optimized results were obtained by balancing the basicity and the amount of the alcohol additive: 3 mol % of the copper catalyst and 40 mol % of TFE at −40 °C gave 96 % yield and 88 % *ee* (Table 1, entry 7). Alternatively, **3aa** could be obtained in 91 % yield and 89 % *ee* using a less basic catalyst, $CuOCH(CF_3)_2$ (5 mol %), derived from more acidic hexafluoroisopropanol (HFIP; pK_a in DMSO = 17.9) (Table 1, entry 8).[11] Lithium was not essential in this reaction, and comparable results were obtained (82 % yield and 88 % *ee*) using a lithium-free copper alkoxide catalyst prepared from mesitylcopper (3 mol %) and excess TFE (43 mol %). On the other hand, a markedly lower yield was obtained when using CF_3CH_2OLi as a catalyst without any copper source (3 mol % *t*BuOLi and 43 mol % TFE; 47 % yield), indicating the critical role of copper in promoting this aldol reaction.

Aromatic aldehydes are even more challenging substrates, because the β-aryl-β-hydroxyynone products have a greater susceptibility to both the retro-aldol reaction and dehydration than β-alkyl-β-hydroxyynones.[12] Indeed, the optimized conditions for aliphatic aldehydes were unsatisfactory for benzaldehyde (**1e**) (Table 2, entries 1 and 2). Excess amounts of alcohol were added to more effectively suppress the retro-aldol reaction. Using 2 equiv of TFE and 5 mol % of catalyst, product **3ea** was obtained in quantitative yield and 93 % *ee* (Table 2, entry 3). The optimization studies shown in Tables 1 and 2 demonstrated the critical importance of the balance between the basicity of the catalyst (to promote the aldol reaction) and the amount of alcohol (to suppress the retro-aldol reaction).

Table 2: Optimization of Cu^I alkoxide-catalyzed asymmetric aldol reaction of an aromatic aldehyde.[a]

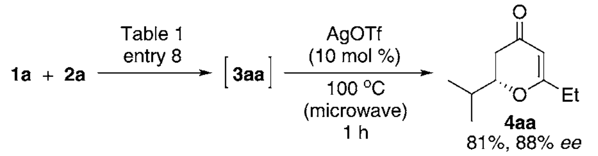


Entry	R	*x*	*y*	Yield [%][b]	*ee* [%]
1	CF_3CH_2	3	40	70	79
2[c]	$(CF_3)_2CH$	5	5	80	61
3[d]	CF_3CH_2	5	200	100	93

[a] CuOR catalyst was prepared from $CuClO_4\cdot 4\,CH_3CN$ and LiOR (1:1). Reaction time was 36 h for entries 1 and 2, and 72 h for entry 3. [b] Determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c] At −30 °C. [d] Using 3 equiv of **2a**.

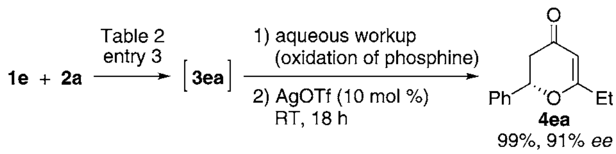
Having established the optimized conditions for the aldol reaction step, we next investigated the oxy-Michael reaction step. Using purified aldol product **3aa**, we screened Lewis acids and identified AgOTf[8c] and AuCl[8a] as excellent catalysts. The reaction rate was significantly enhanced under microwave conditions (100 °C, 1 h). CuOTf also promoted the oxy-Michael reaction, but the reaction rate was lower than with AgOTf and AuCl.

The optimized conditions for the aldol reaction and oxy-Michael reaction were then combined for the sequential dihydropyranone synthesis (Scheme 2). After the aldol reaction, using 5 mol % of $CuOCH(CF_3)_2$ and HFIP (Table 1, entry 8), was complete, AgOTf (10 mol %) was added and the



Scheme 2. Sequential catalytic enantioselective aldol-oxy-Michael reaction of an aliphatic aldehyde. OTf = triflate.

mixture was heated by microwave irradiation at 100 °C for 1 h. Cyclized product **4aa** was obtained in 81 % yield and 88 % *ee*. The enantiomeric excess of **4aa** was slightly lower (86 %) when using $CuOCH_2CF_3$ and TFE conditions for the aldol reaction (Table 1, entry 7). For the more sensitive aldol product **3ea**, derived from an aromatic aldehyde, the sequential one-pot procedure was not successful. Aqueous workup after the aldol reaction involving oxidation of the phosphine by dilute aqueous H_2O_2 was found to be crucial in this case. Thus, an AgOTf-catalyzed oxy-Michael reaction using crude **3ea** at room temperature produced **4ea** in 99 % yield and 91 % *ee* (Scheme 3).

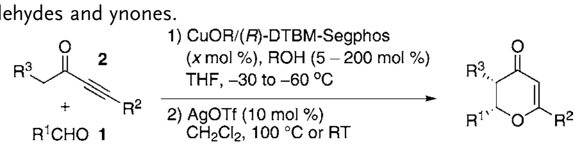


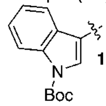
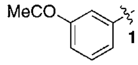
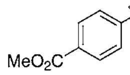
Scheme 3. Sequential catalytic enantioselective aldol-oxy-Michael reaction of an aromatic aldehyde. OTf = triflate.

The substrate scope of the sequential dihydropyranone synthesis was investigated under the optimized conditions (Table 3). The method was applicable to both aliphatic and aromatic aldehydes. Of particular note, the reaction was effective on linear aldehyde **1d**, which is susceptible to self-condensation under basic conditions (Table 3, entry 4). Both ketone and ester functionalities were tolerated (Table 3, entries 11 and 12). For enal **1j**, 1,2-addition to the aldehyde moiety was the exclusive pathway (Table 3, entry 13). The range of functional ynones was also broad. Specifically, ynone **2c**, containing a free hydroxy group, produced **4cc** in high yield and enantioselectivity (Table 3, entry 6). The method was also applicable to α-substituted ynones. The use of ethyl ketone **2e** promoted the facile synthesis of 2,3,6-trisubstituted dihydropyranone **4ce**, affording the product with high diastereo- and enantioselectivity (Table 3, entry 14, 6.7:1 d.r., 85 % *ee*, 63 % yield). Therefore, the current method, which starts from stable and easily accessible ynones, is noteworthy with regard to the synthetic value of the products, broad substrate scope, easy operation under mild reaction conditions, and excellent chemoselectivity. The products, enantiomerically enriched 2,6-disubstituted dihydropyranones, are generally difficult to synthesize through previously established catalytic asymmetric hetero-Diels–Alder reactions using the corresponding Danishefsky-type siloxy dienes.[13]

In summary, we have developed a facile and general catalytic asymmetric method for the synthesis of enantiomerically-enriched substituted dihydropyranones. The process involves two sequential steps with unstable aldol intermediates derived from ynones. Three main characteristics of the chiral Cu^I-conjugated base catalyst favorably contributed to the success of the reaction: 1) alkyne affinity leading to chemoselective enolization, 2) tuneable basicity through the alkoxide, and 3) tolerance of excess protic agents that are needed to suppress the retro-aldol reaction. In addition, soft electrophilic π-activation of the C≡C bond by the Ag^I catalyst was also critical. Expansion of these concepts to other important bond formations is ongoing.

Table 3: Catalytic asymmetric synthesis of dihydropyranones from aldehydes and ynones.



Entry	Aldehyde: R^1	Ynone: R^2, R^3	*x*	Cond.[a]	Prod.	Yield [%][b]	*ee* [%]
1	*i*Pr (**1a**)	Et, H (**2a**)	5	A[c]	**4aa**	81	88
2	*c*Hex (**1b**)	Et, H (**2a**)	5	A[c]	**4ba**	75	88
3[d]	*t*Bu (**1c**)	Et, H (**2a**)	3	A	**4ca**	88	93
4	$Ph(CH_2)_2$ (**1d**)	Et, H (**2a**)	3	A[e]	**4da**	55	75
5	*t*Bu (**1c**)	Ph, H (**2b**)	3	A[f]	**4cb**	65	95
6	*t*Bu (**1c**)	$(CH_2)_2OH$, H (**2c**)	3	A[f]	**4cc**	73	93
7	Ph (**1e**)	Et, H (**2a**)	5	B	**4ea**	99	91
8[g]	Ph (**1e**)	Me, H (**2d**)	5	B	**4ed**	94	90
9	2-naph (**1f**)	Et, H (**2a**)	5	B	**4fa**	89	88
10	 **1g**	Et, H (**2a**)	5	B[h]	**4ga**	75	83
11	 **1h**	Et, H (**2a**)	3	B[i]	**4ha**	56	87
12	 **1i**	Et, H (**2a**)	3	B[i]	**4ia**	61	93
13	(*E*)-PhCH=CH (**1j**)	Et, H (**2a**)	5	B	**4ja**	63	76
14[j]	*t*Bu (**1c**)	Ph, Me (**2e**)	3	A[k]	**4ce**	63	85

[a] Conditions: A = $CuOCH_2CF_3$/(*R*)-DTBM-Segphos (3 mol %) and CF_3CH_2OH (40 mol %) in THF at −40 °C for 20 h (for the aldol reaction); AgOTf (OTf = triflate; 10 mol %) in CH_2Cl_2 at 100 °C (microwave) for 1 h (for cyclization). B = $CuOCH_2CF_3$/(*R*)-DTBM-Segphos (5 mol %) and CF_3CH_2OH (200 mol %) in THF at −60 °C for 72 h (for the aldol reaction); AgOTf (10 mol %) in CH_2Cl_2 at RT for 18 h (for cyclization). See the Supporting Information for details. [b] Yield of isolated product. [c] Conditions given in Table 1, entry 8 were used. [d] Performed on a 10 mmol scale. [e] −60 °C (for the aldol reaction). [f] At RT for 18 h (for cyclization). [g] The absolute configuration was determined to be *S*. [h] AuCl (10 mol %) in CH_2Cl_2 at RT for 72 h (for cyclization). [i] $CuOCH_2CF_3$/(*R*)-DTBM-Segphos (3 mol %) and CF_3CH_2OH (120 mol %; for the aldol reaction). [j] Diastereomeric ratio of the product = 6.7:1 (*cis*/*trans*). [k] At −60 °C in THF/DMF (1:1) for 48 h (for the aldol reaction); using 20 mol % of AgOTf at RT for 18 h (for cyclization). *c*Hex = cyclohexyl, 2-naph = 2-naphthyl.

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[12] The pK_a (in DMSO) values were calculated using Jaguar version 7.0, which revealed that the hydroxy group in **3ea** is significantly more acidic than that of **3aa**. See the Supporting Information.

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