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Asymmetric Catalysis

Direct Enantioselective Three-Component Synthesis of Optically Active Propargylamines in Water

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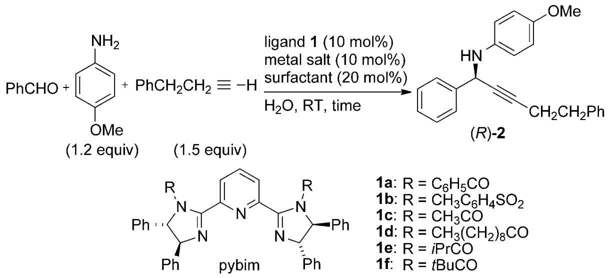
Abstract: An enantioselective three-component reaction of aldehydes, amines, and alkynes in water by using a bis(imidazoline)–Cu^I catalysts having a hydrophobic substituent and sodium dodecyl sulfate as a surfactant was developed. The reaction was applied to a broad range of aldehydes and alkynes to give optically active propargylamines with excellent yields (up to 99%) and enantiomeric excesses (up to 99% *ee*).

Optically active propargylamines and their derivatives have been proven to be useful building blocks for the preparation of various natural products[1] and biologically active compounds.[2] Their broad utility has prompted considerable interest in developing asymmetric methods for their preparation under environmentally friendly conditions. In this context, the enantioselective three-component reaction of a carbonyl compound, an amine, and an alkyne is one of the most straightforward approaches for the synthesis of chiral propargylamines.[3,4] Water is a desirable solvent for organic synthesis due to its safety, low cost, and environmentally benign character.[5] To date, only little attention has been paid to performing enantioselective three-component reactions of carbonyl compounds, amines, and alkynes in water.[6,7] The reaction includes an equilibrium to produce the product and water as a by-product; therefore, it is difficult to carry out the propargylamine synthesis in water by using the three-component reaction. The best results for this reaction were described by Li and co-workers who reported that the conversion of preprepared imines and phenylacetylene by using a pybox–Cu^I catalyst and stearic acid as a surfactant in water gave the desired products with moderate to high enantioselectivities (35–97% *ee*).[6c] Despite this impressive progress, the alkyne substrate was restricted to aryl-substituted alkynes. Therefore, it is desirable to extend the scope of the reaction to aliphatic alkynes in water. Recently, we developed a copper–bis(imidazoline)-catalyzed three-component synthesis of optically active propargylamines from aldehydes, amines and aliphatic alkynes in organic solvents.[8,9] We expect that the highly tunable bis(imidazoline) structure can be applied to an enantioselective reaction in water. Herein, we report a highly enantioselective direct three-component reaction of aldehydes, amines, and aliphatic alkynes by using a chiral bis(imidazoline)–Cu^I catalyst in water.

We first examined the reaction of benzaldehyde, *p*-anisidine (1.2 equiv) and 4-phenylbutyne (1.5 equiv) by using chiral bis(imidazoline)s **1a**–**f** and a metal salt. The results are shown in Table 1.

Table 1. Enantioselective three-component reaction of benzaldehyde, *p*-anisidine, and 4-phenylbutyne by using various chiral ligands.



Entry	1	Metal salt	Surfactant	Time [h]	Yield [%]	*ee* [%]
1	**1 a**	CuOTf[a]	–	84	1	45
2	**1 a**	CuOTf[a]	SDS	48	41	88
3	**1 b**	CuOTf[a]	SDS	48	12	43
4	**1 c**	CuOTf[a]	SDS	48	63	95
5	**1 d**	CuOTf[a]	SDS	48	37	93
6	**1 e**	CuOTf[a]	SDS	48	89	94
7	**1 f**	CuOTf[a]	SDS	18	99	98
8	**1 f**	CuOTf[a]	CTAB	18	0	–
9	**1 f**	CuOTf[a]	Triton X-100	18	17	98
10	**1 f**	CuOTf[a]	sodium laurate	18	0	–
11	**1 f**	$Cu(OTf)_2$	SDS	18	96	98
12[b]	**1 f**	CuOTf[a]	SDS	156	94	98
13	**1 f**	CuDS[c]	–	18	91	98
14[d]	**1 f**	CuOTf[a]	–	72	29	98

[a]CuOTf·1/2 toluene was used. [b] **1 f** (5 mol%) and CuOTf·1/2 toluene (5 mol%) was used. [c] SDS = sodium dodecyl sulfate. [d] Reaction performed in CH_2Cl_2.

The reaction in water by using 10 mol% of a *N*-benzoyl 1,3-bis(imidazolin-2-ly)pyridine (*N*-Bz-pybim, **1 a**)–CuOTf·1/2 toluene complex gave product **2** in a low yield with moderate enantioselectivity (entry 1). During the reaction process, the reactants were insoluble in water. Therefore, we assumed that the reaction could be accelerated by using a surfactant, which forms a colloidal dispersion with the substrates and the catalyst. Ini-

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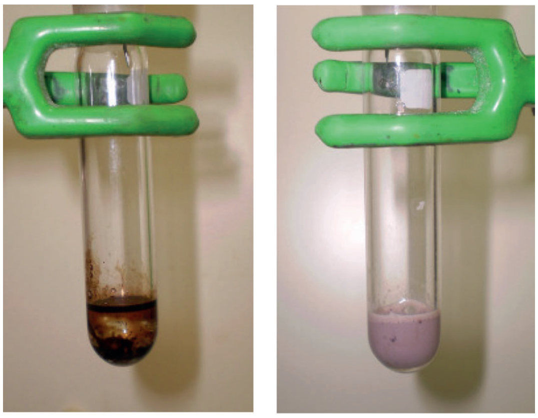
tially, sodium dodecyl sulfate (SDS) was used as a surfactant for the reaction, and after its addition the reaction mixture was homogenized (Figure 1).


PhCHO + $PMPNH_2$ + alkyne + **1f** + CuOTf·1/2 toluene in water

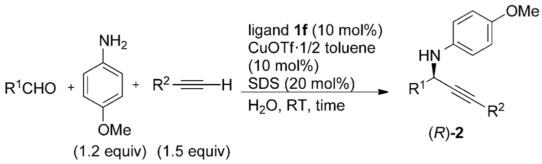
PhCHO + $PMPNH_2$ + alkyne + **1f** + CuOTf·1/2 toluene + SDS in water

Figure 1. Homogenized reaction mixture after the addition of SDS.

Using SDS improved the chemical yield and enantioselectivity of the product (entry 1 vs. 2). When the reaction was complete, the addition of NaCl to the reaction mixture easily caused a phase separation to the aqueous and organic phase by a salting-out effect. Next, optimization experiments for the fine-tuning of the N-substituents of the imidazoline ligands were carried out, and a pivaloyl group was found to be the best substituent to give product **2** in a high yield with high enantioselectivity (entries 2–7). In the presence of ligand **1 f**, other cationic, neutral, or anionic surfactants, such as cetyltrimethylammonium bromide (CTAB), polyoxyethylene *p*-(1,1,3,3-tetramethylbutyl)phenyl ether (Triton-X100), and sodium laurate, did not give good results (entries 7–10). Although the reaction by using $Cu(OTf)_2$ instead of the CuOTf·1/2 toluene complex afforded **2** in a good yield with high enantioselectivity, *p*-methoxylnitrobenzene was formed as a by-product as well, which was obtained from the oxidation of *p*-anisidine by $Cu(OTf)_2$, which then in turn was reduced to the copper(I) species (entry 11).[10] The catalyst loading was successfully reduced to 5 mol% without any loss in enantioselectivity (entry 12). When using $Cu(OSO_3C_{12}H_{25})$ as a copper species without SDS, the reaction mixture formed a colloidal dispersion to afford the desired product **2** in high yield with high enantioselectivity (entry 13). On the other hand, performing the reaction in CH_2Cl_2 by using **1 f**–Cu^I gave **2** with the same enantiomeric excess but in a low yield (entry 14).

Encouraged by these results, we then studied the scope and limitations of the bis(imidazoline) **1 f**-catalyzed three-component reaction of various aldehydes and alkynes by using SDS in aqueous micellar solutions. The results are summarized in Table 2. The reaction of various substituted alkynes with benzaldehyde afforded products **2**–**13** in high yields with high enantioselectivity (entries 1–12). In the reaction with phenylacetylene, both electron-rich and -poor aldehydes performed well, giving the desired products **14**–**20** with 86–99% *ee* (entries 13–19). A maximum of 99% *ee* was obtained in the reaction with *m*-methoxy- or *m*-chlorobenzaldehyde (Table 2, entries 15 and 16). The chemical yield was excellent in most cases. With cyclohexanecarboxaldehyde, the desired product **21** was obtained in a good yield with high enantioselectivity (entry 20), whereas the reaction in CH_2Cl_2 by using **1 a**–CuOTf gave **21** in 13% yield with 72% *ee*.

Table 2. Enantioselective three-component reaction of various aldehydes and alkynes by using **1 f**–Cu^I.

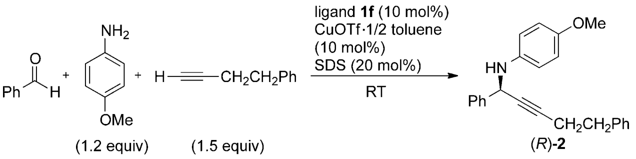


Entry	Aldehyde [R^1]	Alkyne [R^2]	Product	Time [h]	Yield [%]	*ee* [%]
1	Ph	CH_2CH_2Ph	**2**	18	99	98
2	Ph	$CH_2CH_2CH_3$	**3**	36	80	97
3	Ph	$(CH_2)_3CH_3$	**4**	48	93	97
4	Ph	$(CH_2)_5CH_3$	**5**	24	87	99
5	Ph	$(CH_2)_7CH_3$	**6**	48	93	97
6[a]	Ph	cyclopropyl	**7**	96	90	95
7	Ph	cyclopentyl	**8**	66	91	95
8	Ph	cyclohexyl	**9**	66	76	98
9	Ph	CH_2CH_2Br	**10**	66	62	98
10	Ph	CH_2CH_2OH	**11**	72	77	96
11	Ph	$C(CH_3)_2OH$	**12**	72	60	90
12	Ph	Ph	**13**	48	99	98
13	2-$MeOC_6H_4$	CH_2CH_2Ph	**14**	24	85	90
14	2-ClC_6H_4	CH_2CH_2Ph	**15**	24	95	98
15	3-$MeOC_6H_4$	CH_2CH_2Ph	**16**	24	86	99
16	3-ClC_6H_4	CH_2CH_2Ph	**17**	48	80	99
17	4-$MeOC_6H_4$	CH_2CH_2Ph	**18**	72	67	86
18[b]	4-ClC_6H_4	CH_2CH_2Ph	**19**	48	80	98
19	1-naphthyl	CH_2CH_2Ph	**20**	96	91	92
20	cyclohexyl	CH_2CH_2Ph	**21**	48	66	98

[a] Alkyne (3.0 equiv) was used. [b] Reaction was carried out at 40 °C.

Tap water and seawater are attractive and environmentally friendly reaction media for organic synthesis.[11] Therefore, we also examined the reaction in tap water or seawater that was taken directly from the Pacific Ocean (Scheme 1). In these aqueous solutions, the reaction proceeded well, affording product **2** in high yield with high enantioselectivity.

After the reaction, most of catalyst **1 f** could be recovered by column chromatography and reused without further purifi-



in water: 99%, 98% *ee*
in tap water: 87%, 98% *ee*
in seawater: 73%, 96% *ee*

Scheme 1. Enantioselective three-component reaction in tap water and seawater.

cation. The reaction by using recovered **1 f** afforded product **2** in 83 % yield with 98 % *ee*.

The reaction of benzaldehyde, *p*-anisidine, and 4-phenylbutyne by using Cu($OSO_3C_{12}H_{25}$) afforded almost the same result as the reaction by using CuOTf and SDS (Table 1, entry 7 vs. 13). Therefore, the three-component reaction could be activated by **1 f**–Cu($OSO_3C_{12}H_{25}$) complexes.[12] Furthermore, the substituent on the nitrogen atom of the imidazoline ligand dramatically influenced the yield of the product and the reactivity of the reaction. These results show that the hydrophobic effects of the substituent on the imidazoline ligand and the copper salt are important for the formation of a colloidal dispersion and the enhancement of their reactivity (Figure 2).

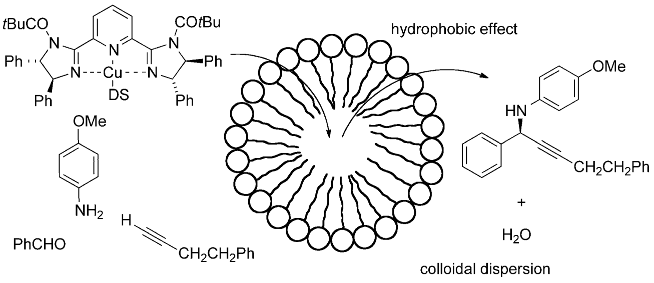


Figure 2. Three-component reaction in water by using a hydrophobic chiral catalyst.

There are several reports on the reaction mechanism for the enantioselective alkynylation of imines by using a copper(I) salt[13] in which the copper salt forms a pentacoordinated (distorted trigonal bipyramid) complex. On the basis of these considerations, the assumed transition states for the enantioselective alkynylation of imines by using **1 f**–Cu^I are shown in Figure 3. The copper–acetylide attacks the imine from the *Si* face of the imine to provide the (*R*)-propargylamine. Further studies are required to fully elucidate the mechanistic details of the alkynylation.

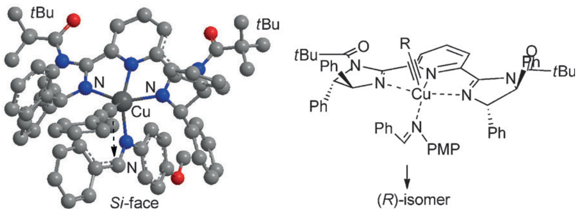


Figure 3. Proposed transition state for the alkynylation of an imine by using **1 f**-Cu^I.

In conclusion, we have developed an enantioselective three-component reaction of aldehydes, amines, and alkynes by using a bis(imidazoline)–Cu^I catalysts having a hydrophobic substituent and SDS as a surfactant. The reaction was screened for a broad range of aldehydes and alkynes. This process offers a simple and environmentally friendly route to optically active propargylamines. Further experiments to study the scope of this process and potential applications of the bis(imidazoline) catalyst in other reactions are in progress.

Experimental Section

General procedure for the enantioselective three-component reaction of aldehydes, amines, and alkynes by using 1 f–Cu^I

A solution of bis(imidazoline) **1 f** (0.025 mmol, 10 mol %), CuOTf·1/2toluene (0.025 mmol, 10 mol %) and SDS (0.05 mmol, 20 mol %) in ultra-pure water (0.6 mL) was stirred for 1 h at room temperature (23–25 °C). Ultra-pure water (0.8 mL), an aldehyde (0.25 mmol), *p*-anisidine (0.30 mmol) and an alkyne (0.37 mmol) were added, and the whole reaction mixture was stirred at room temperature. After completion of the reaction monitored by TLC, NaCl (100 mg) was added. Water was removed by decantation then the organic phase was purified over silica gel by column chromatography (CH_2Cl_2/hexane) to give propargylamines.

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Keywords: alkynylation · enantioselectivity · propargylamines · three-component reaction · water

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