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Enantioselective Direct-Addition of Terminal Alkynes to Imines Catalyzed by Copper(I)pybox Complex in Water and in Toluene

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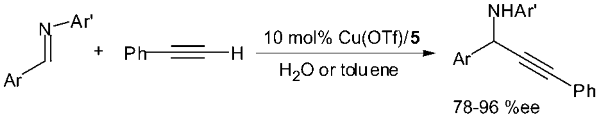
Catalytic asymmetric reactions provide the most important methods for synthesizing optically active molecules.[1] Catalytic asymmetric C−C bond formations are among the most challenging of these, and various highly enantioselective reactions have been developed in the past decade.[2] On the other hand, while there has been a considerable interest in developing C−C bond-formation reactions that are tolerant toward water, related catalytic asymmetric C−C bond formation remained largely unexplored until Engberts and co-workers reported a highly enantioselective Lewis acid-catalyzed Diels−Alder reaction in water recently.[3] Subsequently, major progress has been made in asymmetric palladium-catalyzed Trost−Tsuji reactions by Uozumi,[4] Mukaiyama-aldol reaction by Kobayashi,[5] carbonyl allylation by Loh,[6] cyclopropanation by Nishiyama,[7] and rhodium-catalyzed[8] arylboronic acid reactions by Hayashi and others.[9]

Optically active propargylamines are important synthetic intermediates for the synthesis of various nitrogen compounds and a structural feature of many biologically active compounds and natural products.[10] The most reliable and efficient methods for the preparation of optically active propargylic amines still remains the addition of an appropriate organometallic reagent to chiral imine derivatives.[11] Recently, we described a Grignard-type direct addition of alkyne to imines[12] catalyzed by ruthenium/copper via C−H activation[13] in water or under neat conditions. Independently, Carreira and co-worker reported a similar coupling by using an iridium catalyst in toluene or under neat conditions.[14] However, methods for the catalyzed preparation of optically active propargylic amines are still very limited.[15] During our investigation, it was observed that CuBr alone also provided the desired product albeit in low conversions.[16] We hypothesized that, although it is a disappointment at first glance, the low conversion by using CuBr as the catalyst may in fact provide us with a rare opportunity to develop highly efficient enantioselective alkyne−imine additions. Herein, we wish to report the preliminary results of a highly enantioselective copper-catalyzed alkyne−imine (generated in situ from aldehyde and amine) addition in water and in toluene (Scheme 1).

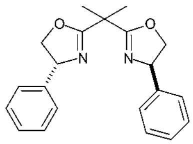
Scheme 1



First, we examined a variety of chiral compounds as ligands in the addition reaction of phenylacetylene with *N*-benzylideneaniline with 10 mol % of CuBr and CuOTf as the catalysts. The vast majority of those experiments resulted in disappointing enantioselectivities. During the past two decades chiral copper−bis(oxazoline) complexes have been shown to be effective as catalysts for enantioselective reactions.[17] Thus, chiral bis(oxazolinyl) ligands **1**−**5** were examined (Table 1).

Table 1. Effect of Conditions on the Enantioselectivity of the Phenylacetylene *N*-Benzylindeneaniline Addition

entry	catalyst	ligand	temp (°C)/ time (d)	solvent	o.r./ee%
1	CuBr	**1**	40/1	H_2O	<5
2	CuBr	**2**	40/1	H_2O	<5
3	CuBr	**3**	40/1	H_2O	(+) 24
4	CuBr	**4**	40/1	H_2O	(−) 19
5	CuBr	**5**	40/1	H_2O	(+) 18
6	CuOTf	**3**	22/4	H_2O	(+) 45
7	CuOTf	**4**	22/4	H_2O	(+) 14
8	CuOTf	**5**	22/4	H_2O	(+) 83
9	CuOTf	**3**	45/1	H_2O	(+) 44
10	CuOTf	**4**	45/1	H_2O	(+) 9
11	CuOTf	**5**	45/1	H_2O	(+) 78
12	CuOTf	**3**	22/4	toluene	(+) 40
13	CuOTf	**4**	22/4	toluene	(+) 21
14	CuOTf	**5**	22/4	toluene	(+) 96



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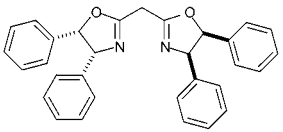

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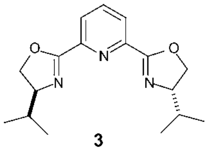

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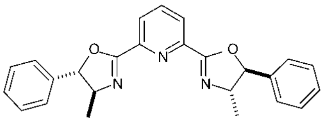

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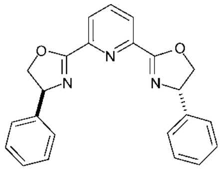

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It was found that the desired enantioselective addition product was formed in low % ee by using the bidentate bis(oxazoline) (box) **1** or **2** with CuBr in water. On the other hand, the use of the tridentate bis(oxazolinyl)pyridines (pybox) such as **3**, **4**, **5** led to increased enantioselectivities. The optimal enantioselectivity of addition adducts was obtained with **5**−CuBr complex (90% conversion and 24% ee in water). The use of copper(I) triflate complex instead of CuBr afforded the product with both high reactivity and enantioselectivity (90% conversion, 83% ee for **5** in water), whereas the corresponding **5**−Cu(I) SbF_6 complex (although

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Table 2. Enantioselectivity of the Alkyne−Imine Addition in Toluene

entry	aldehyde	aniline	temp (°C)/time (d)	yield (%)	o.r./ee%
1	PhCHO	$PhNH_2$	22/4	78	(+) 96
2	PhCHO	$PhNH_2$	35/2	83	(+) 93
3	4-MeC_6H_4CHO	$PhNH_2$	35/2	85	(+) 92
4	4-EtC_6H_4CHO	$PhNH_2$	22/4	70	(+) 96
5	4-EtC_6H_4CHO	$PhNH_2$	35/2	73	(+) 95
6	4-ClC_6H_4CHO	$PhNH_2$	22/4	85	(+) 94
7	4-ClC_6H_4CHO	$PhNH_2$	35/2	90	(+) 92
8	4-BrC_6H_4CHO	$PhNH_2$	22/4	87	(+) 94
9	4-BrC_6H_4CHO	$PhNH_2$	35/2	90	(+) 92
10	4-PhC_6H_4CHO	$PhNH_2$	22/4	81	(+) 94
11	4-PhC_6H_4CHO	$PhNH_2$	35/2	85	(+) 90
12	2-NaphCHO	$PhNH_2$	22/4	63	(+) 88
13	2-NaphCHO	$PhNH_2$	35/2	67	(+) 82
14	4-$CF_3C_6H_4CHO$	$PhNH_2$	22/4	71	(+) 93
15	PhCHO	4-$BrC_6H_4NH_2$	35/2	93	(+) 91
16	PhCHO	4-$ClC_6H_4NH_2$	35/2	92	(+) 91
17	PhCHO	4-$MeC_6H_4NH_2$	35/2	93	(+) 94

Table 3. Enantioselectivity of the Alkyne−Imine Addition in Water

entry	aldehyde	aniline	temp (°C)/time (d)	yield (%)	o.r./ee%
1	PhCHO	$PhNH_2$	22/4	71	(+) 84
2	PhCHO	$PhNH_2$	35/2	77	(+) 80
3	4-MeC_6H_4CHO	$PhNH_2$	35/2	86	(+) 81
4	4-EtC_6H_4CHO	$PhNH_2$	22/4	68	(+) 89
5	4-EtC_6H_4CHO	$PhNH_2$	35/2	68	(+) 78
6	4-ClC_6H_4CHO	$PhNH_2$	22/4	70	(+) 87
7	4-ClC_6H_4CHO	$PhNH_2$	35/2	74	(+) 85
8	4-BrC_6H_4CHO	$PhNH_2$	22/4	63	(+) 87
9	4-BrC_6H_4CHO	$PhNH_2$	35/2	74	(+) 85
10	4-PhC_6H_4CHO	$PhNH_2$	22/4	48	(+) 84
11	4-PhC_6H_4CHO	$PhNH_2$	35/2	56	(+) 82
12	2-NaphCHO	$PhNH_2$	22/4	57	(+) 86
13	2-NaphCHO	$PhNH_2$	35/2	65	(+) 78
14	4-$CF_3C_6H_4CHO$	$PhNH_2$	22/4	56	(+) 87
15	PhCHO	4-$BrC_6H_4NH_2$	35/2	82	(+) 83
16	PhCHO	4-$ClC_6H_4NH_2$	35/2	77	(+) 84
17	PhCHO	4-$MeC_6H_4NH_2$	35/2	68	(+) 91

it had a similar enantioselectivity) was much less reactive (20% conversion, and 79% ee in water). The reaction of 1.5 equiv of phenylacetylene with *N*-benzylideneaniline in water in the presence of 10 mol % Cu(I)OTf and 10 mol % chiral pybox **5** at 22 °C for 4 days afforded the adduct in about 71% yield and 84% ee. In toluene, the enantioselectivity and yield were further increased (78% isolated yield and 96% ee).[18] Interestingly, the use of Cu(I)OTf instead of Cu(I)Br also switched the enantioselectivity of the product (compare entries 4, 7, 10).

Subsequently, a variety of substrates were examined by using the combination of Cu(I)OTf/**5**, the results of which are summarized in Tables 2 and 3. In all cases, the reactions took place smoothly giving a (+)-propargylamine in high enantioselectivity and good yields. The reactions in toluene provided slightly higher yields and enantioselectivities than in water.

In conclusion, we have developed a highly enantioselective copper(I)-catalyzed direct alkyne−imine addition. The process is simple and provides a diverse range of propargylic amines in high ee and good yield. The scope, mechanism, and synthetic application of this novel enantioselective reaction as well as other C−C bond formations via C−H activation are under investigation.

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Supporting Information Available: Representative experimental procedure for enantioselective alkyne−imine additions and the characterization data for all addition products (PDF). This material is available free of charge via the Internet at http:/pubs.acs.org.

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(18) The error limits are approximately 3% for isolated yields and 2% for % ee.

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