

Copper-Catalyzed Enantioselective Three-Component Synthesis of Optically Active Propargylamines from Aldehydes, Amines, and Aliphatic Alkynes

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Optically active propargylamines are important synthetic intermediates for the preparation of various natural products^[1] and biologically active compounds.^[2] A typical route to prepare chiral propargylamines is the stereoselective addition of terminal alkynes to imines.^[3] Since the pioneering work of Li and co-workers on the highly enantioselective three-component reaction of aldehydes, amines, and alkynes by using 1,3-bis(oxazolin-2-yl)pyridine ligands (pybox)^[4] and a copper salt to give optically active propargylamines,^[5] remarkable progress has been made in the copper-catalyzed three-component reaction because of the simplified operation.^[6,7] Although there are many reports on the highly enantioselective addition of aryl- and silyl-substituted alkynes with in situ generated imines, the three-component reaction with aliphatic terminal alkynes remains unsolved probably due to the low steric hindrance of alkyl alkynes. To the best of our knowledge, there exist only a handful of examples of highly enantioselective three-component reactions of aldehydes, amines, and aliphatic alkynes with chiral catalysts.^[6a,c,f,g] Recently, Singh and Bisai reported the highly enantioselective synthesis of propargylamines through the three-component reaction by using bulky pybox–Cu^I catalysts; however, the reaction with aliphatic alkynes afforded products with lower enantioselectivity (up to 87% enantiomeric excess (*ee*)) than that with aryl-substituted alkynes.^[6g] The best result for this type of reaction with an aliphatic alkyne was reported by Carreira and co-workers, in which an enantioselective three-component reaction of 2-methylbutanal, dibenzylamine, and 1-hexyne as an aliphatic alkyne

with a chiral pinap–Cu^I catalyst (pinap = [2-(diphenylphosphino)-1-naphthalenyl]-*N*-(1-phenylethyl)-1-phthalazamine) gave a product with 94% *ee*.^[6c] Therefore, expanding the scope of catalytic enantioselective three-component reactions with respect to both the chiral catalyst and the substrate would be highly desirable. On the other hand, we recently developed chiral bis(imidazoline)–Cu^{II} catalysts as highly tuneable chiral catalysts.^[8,9] Herein, our ongoing interest was extended to a highly enantioselective three-component reaction of aldehydes, amines, and aliphatic alkynes by using a chiral bis(imidazoline)–Cu^I catalyst.

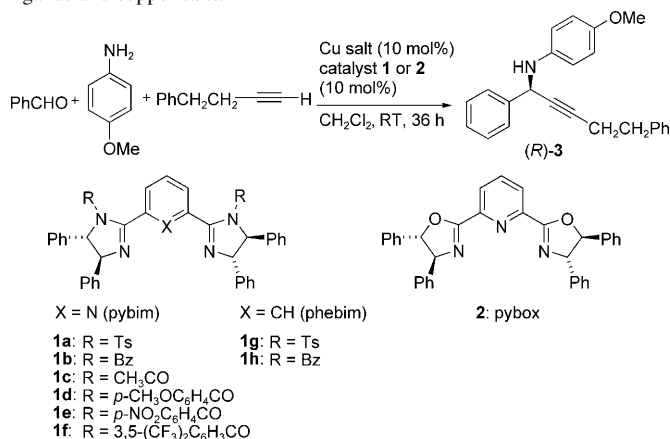
We first examined the reaction of benzaldehyde, *p*-anisidine, and 4-phenylbutyne as the aliphatic alkyne with Cu^I catalysts of chiral bis(imidazoline)s **1a–1h**. The results are shown in Table 1. When the reaction was carried out with *N*-tosyl 1,3-bis(imidazolin-2-yl)pyridine (*N*-Ts-pybim, **1a**, 10 mol %)^[10] as the ligand, **1a**–(CuOTf)₂·toluene complex gave product **3** with moderate enantioselectivity, whereas, the reaction with *N*-benzoyl pybim, **1b**–(CuOTf)₂·toluene complex afforded **3** in 93% yield with 98% *ee* (Table 1, entries 1 and 2). After fine-tuning various substituents on the nitrogen in the imidazolines, the benzoyl group was found to be the best substituent to obtain a high yield with high enantioselectivity (Table 1, entries 3–6). On the other hand, the desired enantioselective addition product was formed in low enantioselectivity by using the bidentate 1,3-bis(imidazolin-2-yl)benzene (Phebim) with (CuOTf)₂·toluene in CH₂Cl₂ (Table 1, entries 7 and 8). The reaction with the pybox ligand **2** afforded **3** with good enantioselectivity, but in low yield (Table 1, entry 9). The reaction with the use of various copper salts, such as CuCl, CuI, [Cu(CH₃CN)₄]PF₆, and Cu(OTf)₂, did not afford good results (Table 1, entries 10–13).

Optimization experiments, for both amines and solvents, were carried out to improve both the yield and enantioselectivity of the reaction in the presence of **1b**–(CuOTf)₂·toluene complex (Table 2), the reaction with *p*-anisidine in CH₂Cl₂ was very effective for the three-component synthesis of propargylamines (Table 2, entry 1).

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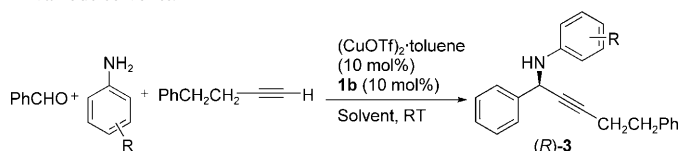
Table 1. Enantioselective three-component reaction with various chiral ligands and copper salts.^[a]



Entry	Ligand	Cu salt	Yield [%]	ee [%] ^[b]
1	1a	(CuOTf) ₂ ·toluene	61	84
2 ^[c]	1b	(CuOTf) ₂ ·toluene	93	98
3	1c	(CuOTf) ₂ ·toluene	79	97
4	1d	(CuOTf) ₂ ·toluene	82	95
5	1e	(CuOTf) ₂ ·toluene	38	87
6	1f	(CuOTf) ₂ ·toluene	54	93
7	1g	(CuOTf) ₂ ·toluene	19	22
8	1h	(CuOTf) ₂ ·toluene	71	4
9	2	(CuOTf) ₂ ·toluene	33	82
10	1b	CuCl	trace	—
11	1b	CuI	—	—
12	1b	[Cu(CH ₃ CN) ₄]PF ₆	19	91
13	1b	Cu(OTf) ₂	53	90

[a] Reaction conditions: PhCHO (0.25 mmol), *p*-anisidine (0.3 mmol), 4-phenylbutyne (0.37 mmol), Cu salt (0.025 mmol), **1** (0.025 mmol) at RT for 36 h; OTf = trifluoromethanesulfonate, Ts = tosyl, Bz = benzoyl. [b] ee was determined by HPLC analysis by using chiral columns. [c] Performed at RT for 12 h.

Table 2. Enantioselective three-component reaction with various amines in various solvents.^[a]



Entry	Amine	Solvent	Yield [%]	ee ^[b] [%]
1	<i>p</i> -MeOC ₆ H ₄ NH ₂	CH ₂ Cl ₂	93	98
2	C ₆ H ₅ NH ₂	CH ₂ Cl ₂	38	93
3	<i>o</i> -MeOC ₆ H ₄ NH ₂	CH ₂ Cl ₂	trace	—
4	(PhCH ₂) ₂ NH	CH ₂ Cl ₂	trace	—
5	<i>p</i> -MeOC ₆ H ₄ NH ₂	CHCl ₃	10	92
6	<i>p</i> -MeOC ₆ H ₄ NH ₂	ClCH ₂ CH ₂ Cl	90	98
7	<i>p</i> -MeOC ₆ H ₄ NH ₂	Et ₂ O	75	94
8	<i>p</i> -MeOC ₆ H ₄ NH ₂	toluene	9	83
9	<i>p</i> -MeOC ₆ H ₄ NH ₂	H ₂ O	40	90

[a] Reaction conditions: PhCHO (0.25 mmol), amine (0.3 mmol), 4-phenylbutyne (0.37 mmol), (CuOTf)₂·toluene (0.025 mmol), and **1** (0.025 mmol) at RT for 36 h. [b] ee was determined by HPLC analysis by using chiral columns.

With these optimized conditions, a variety of aldehydes and alkynes were examined by using the combination of **1b**

with (CuOTf)₂·toluene, the results of which are summarized in Table 3. The reaction of imines derived from benzaldehyde and *p*-anisidine with various aliphatic alkynes afforded

Table 3. Enantioselective three-component reaction of various aldehydes and alkynes by using **1b**–Cu^I.^[a]

$\text{R}^1\text{CHO} + \text{p-anisidine} + \text{R}^2\text{C}\equiv\text{CH} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{RT, time}]{(\text{CuOTf})_2\cdot\text{toluene (10 mol\%), 1b (10 mol\%)}} \text{(R)-3-24}$

Entry	Aldehyde (R ¹)	Alkyne (R ²)	Product	<i>t</i> [h]	Yield [%]	ee [%]
1	Ph	CH ₂ CH ₂ Ph	3	12	93	98
2 ^[b]	Ph	CH ₂ CH ₂ CH ₃	4	36	69	95
3 ^[b]	Ph	(CH ₂) ₃ CH ₃	5	84	73	96
4	Ph	(CH ₂) ₅ CH ₃	6	36	83	97
5	Ph	(CH ₂) ₇ CH ₃	7	60	78	96
6	Ph	cyclopropyl	8	36	58	94
7	Ph	cyclopentyl	9	60	75	94
8	Ph	cyclohexyl	10	60	73	96
9	Ph	CH ₂ CH ₂ Br	11	60	65	98
10	Ph	CH ₂ CH ₂ OH	12	72	61	98
11	Ph	C(CH ₃) ₂ OH	13	96	90	94
12	Ph	Ph	14	36	82	95
13	Ph	TMS ^[c]	15	120	28	92
14	2-MeOC ₆ H ₄	CH ₂ CH ₂ Ph	16	84	89	89
15	2-ClC ₆ H ₄	CH ₂ CH ₂ Ph	17	108	86	93
16	3-MeOC ₆ H ₄	CH ₂ CH ₂ Ph	18	84	75	96
17	3-ClC ₆ H ₄	CH ₂ CH ₂ Ph	19	84	62	92
18	4-MeOC ₆ H ₄	CH ₂ CH ₂ Ph	20	36	84	93
19	4-ClC ₆ H ₄	CH ₂ CH ₂ Ph	21	96	74	98
20	4-NO ₂ C ₆ H ₄	CH ₂ CH ₂ Ph	22	84	78	95
21	1-naphthyl	CH ₂ CH ₂ Ph	23	60	84	92
22	(CH ₃) ₂ CHCH ₂	CH ₂ CH ₂ Ph	24	108	39	81

[a] Reaction conditions: aldehyde (0.25 mmol), amine (0.3 mmol), alkyne (0.37 mmol), (CuOTf)₂·toluene (0.025 mmol), and **1** (0.025 mmol) at RT. [b] Alkyne (3 equiv) was used. [c] TMS = trimethylsilyl.

products **3–10** with high enantioselectivity (Table 3, entries 1–8). The reaction with alkynes containing a halogen and a hydroxy group gave good enantioselectivities (Table 3, entries 9–11). The reaction with phenylacetylene as an example of an aryl alkyne also gave product **14** in high yield with high enantioselectivity (Table 3, entry 12). Although the reaction with trimethylsilylacetylene afforded product **15** in low yield, the reaction with 2-methyl-3-butyne-2-ol, which acts as an acetylide anion equivalent, gave product **13** in high yield with high enantioselectivity (Table 3, entry 11 vs. 13). The reaction with various aromatic aldehydes also gave products **16–23** with good enantioselectivity (Table 3, entries 14–21).

In conclusion, we have developed an enantioselective three-component reaction of aldehydes, amines, and aliphatic alkynes catalyzed by C₂-symmetric pybim Cu^I catalysts to give propargylamines in good yields and with high enantioselectivity. This process has many advantages, such as simplified operation and mild reaction conditions. These results open a novel way to synthesize optically active propargylamines. The scope, mechanism, and synthetic application of

the enantioselective reaction as well as other C–C bond formations through C–H activation are under investigation.

Experimental Section

General procedure: A solution of ligand **1b** (0.025 mmol, 10 mol %) and (CuOTf)₂·toluene (0.025 mmol, 10 mol %) in dry CH₂Cl₂ (0.6 mL) was stirred at RT (23–25 °C) for 1 h. An aldehyde (0.25 mmol), *p*-anisidine (0.30 mmol), and an alkyne (0.37 mmol) were added and the whole mixture was stirred at RT. After completion of the reaction, as monitored by TLC, the mixture was concentrated and purified over silica gel by column chromatography (hexane/EtOAc 90:10) yielding pure propargylamines.

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Keywords: alkynylation • asymmetric catalysis • enantioselectivity • imidazolines • multicomponent reactions

- [1] a) M. Konishi, H. Ohkuma, T. Tsuno, T. Oki, G. VanDuyne, J. Clardy, *J. Am. Chem. Soc.* **1990**, *112*, 3715–3716; b) B. M. Trost, C. K. Chung, A. B. Pinkerton, *Angew. Chem.* **2004**, *116*, 4427–4429; *Angew. Chem. Int. Ed.* **2004**, *43*, 4327–4329; c) M. H. Davidson, F. E. McDonald, *Org. Lett.* **2004**, *6*, 1601–1603.
- [2] a) M. A. Huffman, N. Yasuda, A. E. DeCamp, E. J. J. Grabowski, *J. Org. Chem.* **1995**, *60*, 1590–1594; b) G. S. Kauffman, G. D. Harris, R. L. Dorow, P. R. Stone, R. L. Parsons, J. Pesti, Jr., N. A. Magnus, J. M. Fortunak, P. N. Confalone, W. A. Nugent, *Org. Lett.* **2000**, *2*, 3119–3121; c) S. N. Osipov, P. Tsouker, L. Hennig, K. Burger, *Tetrahedron* **2004**, *60*, 271–274.
- [3] For reviews, see: a) B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963–983; b) L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263–4275; c) C.-M. Wei, Z.-G. Li, C.-J. Li, *Synlett* **2004**, 1472–1483; d) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2004**, 4095–4105.
- [4] For a recent review on pybox ligands, see: a) G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2003**, *103*, 3119–3154; for the first report of pybox, see: b) H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo, K. Itoh, *Organometallics* **1989**, *8*, 846–848.
- [5] a) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639; b) C. Wei, J. T. Mague, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5749–5754.
- [6] For the enantioselective three-component reaction of aldehydes, amines, and alkynes, see: a) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, *115*, 5941–5944; *Angew. Chem. Int. Ed.* **2003**, *42*, 5763–5766; b) N. Gommermann, P. Knochel, *Chem. Commun.* **2004**, 2324–2325; c) T. F. Knöpfel, P. Aschwarden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem.* **2004**, *116*, 6097–6099; *Angew. Chem. Int. Ed.* **2004**, *43*, 5971–5973; d) N. Gommermann, P. Knochel, *Synlett* **2005**, 2799–2801; e) N. Gommermann, P. Knochel, *Chem. Commun.* **2005**, 4175–4177; f) J.-X. Ji, J. Wu, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11196–11200; g) A. Bisai, V. K. Singh, *Org. Lett.* **2006**, *8*, 2405–2408; h) Z. Shao, X. Pu, X. Li, B. Fan, A. S. C. Chan, *Tetrahedron: Asymmetry* **2009**, *20*, 225–229; with zinc catalysts, see: L. Zani, T. Eichhorn, C. Bolm, *Chem. Eur. J.* **2007**, *13*, 2587–2600.
- [7] For recent examples of catalytic enantioselective additions of alkynes to imines, see: a) F. Colombo, M. Benaglia, S. Orlandi, F. Uselli, G. Celentano, *J. Org. Chem.* **2006**, *71*, 2064–2070; b) M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem.* **2007**, *119*, 7027–7030; *Angew. Chem. Int. Ed.* **2007**, *46*, 6903–6906; c) J. Liu, B. Liu, X. Jia, X. Li, A. S. C. Chan, *Tetrahedron: Asymmetry* **2007**, *18*, 396–399; d) B. Liu, L. Huang, J. Liu, Y. Zhong, X. Li, A. S. C. Chan, *Tetrahedron: Asymmetry* **2007**, *18*, 2901–2904; e) R. Dodda, C.-G. Zhao, *Tetrahedron Lett.* **2007**, *48*, 4339–4342; f) G. Blay, L. Cardona, E. Climent, J. R. Pedro, *Angew. Chem.* **2008**, *120*, 5675–5678; *Angew. Chem. Int. Ed.* **2008**, *47*, 5593–5596; g) M. Hatano, T. Asai, K. Ishihara, *Tetrahedron Lett.* **2008**, *49*, 379–382; h) M. Irmak, M. M. K. Boysen, *Adv. Synth. Catal.* **2008**, *350*, 403–405.
- [8] a) S. Nakamura, K. Hyodo, Y. Nakamura, N. Shibata, T. Toru, *Adv. Synth. Catal.* **2008**, *350*, 1443–1448; for related recent studies from our group, see: b) N. Hara, S. Nakamura, N. Shibata, T. Toru, *Chem. Eur. J.* **2009**, *15*, 6790–6793; c) S. Nakamura, N. Hara, H. Nakashima, K. Kubo, N. Shibata, T. Toru, *Chem. Eur. J.* **2008**, *14*, 8079–8081; d) S. Nakamura, H. Nakashima, H. Sugimoto, H. Sano, M. Hattori, N. Shibata, T. Toru, *Chem. Eur. J.* **2008**, *14*, 2145–2152; e) S. Nakamura, H. Nakashima, A. Yamamura, N. Shibata, T. Toru, *Adv. Synth. Catal.* **2008**, *350*, 1209–1212; f) S. Nakamura, Y. Sakurai, H. Nakashima, N. Shibata, T. Toru, *Synlett* **2009**, 1639–1642.
- [9] For a recent review on bis(imidazoline)ligands, see: H. Liu, D.-M. Du, *Adv. Synth. Catal.* **2009**, *351*, 489–519, and references therein.
- [10] For pybim ligands, see: a) S. Bhor, G. Anilkumar, M. K. Tse, M. Klawonn, C. Döbler, B. Bitterlich, A. Grotevendt, M. Beller, *Org. Lett.* **2005**, *7*, 3393–3396; b) G. Anilkumar, S. Bhor, M. K. Tse, M. Klawonn, B. Bitterlich, M. Beller, *Tetrahedron: Asymmetry* **2005**, *16*, 3536–3561; c) K. Ma, J. You, *Chem. Eur. J.* **2007**, *13*, 1863–1871; d) S. Enthaler, B. Hagemann, S. Bhor, G. Anilkumar, M. K. Tse, B. Bitterlich, K. Junge, G. Erre, M. Beller, *Adv. Synth. Catal.* **2007**, *349*, 853–860.

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