Chinese Journal of Catalysis 36 (2015) 86–92

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/chnjc

Article (Special Issue on Catalysis in Organic Synthesis)

Enantioselective *N*-propargylation of indoles via Cu-catalyzed propargylic alkylation/dehydrogenation of indolines

Fulin Zhu [a,b], Xiangping Hu [a,*]

[a] *Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning, China*
[b] *University of Chinese Academy of Sciences, Beijing 100049, China*

ARTICLE INFO

Article history:
Received 30 August 2014
Accepted 19 September 2014
Published 20 January 2015

Keywords:
Asymmetric synthesis
Copper
Propargylic substitution
Dehydrogenation
N-propargylindole

ABSTRACT

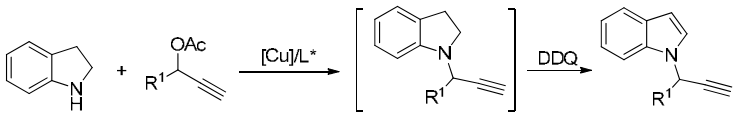
The synthesis of optically active *N*-propargylindoles has been accomplished via the Cu-catalyzed asymmetric propargylic alkylation of indolines with propargylic esters, followed by the dehydrogenation of the resulting *N*-substituted indolines with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The reaction proceeded in good yield with high enantioselectivity under mild conditions using a bulky and structurally rigid tridentate ketimine P,N,N-ligand, and exhibited a broad substrate scope.

1. Introduction

Following of the pioneering works of Hattori et al. [1] and Detz et al. [2] in 2008, there has been significant progress towards the development of Cu-catalyzed asymmetric propargylic substitution reactions [3,4], with numerous *N*- and *C*-based nucleophiles, including primary and secondary amines, enamines and enolates, being identified as suitable reaction partners [5–21]. Despite these advances, several challenging issues still need to be addressed in the Cu-catalyzed asymmetric propargylic substitution reaction. One of the biggest issues with this transformation is the enantioselective *N*-propargylation of indole, in that the direct *N*-propargylation of indole with propargylic esters is effectively impossible because of the weakly acidic nature of the *N*–H group of the indole. Indeed, Detz et al. [9] reported the development of a highly enantioselective Cu-catalyzed propargylation of indole with propargylic acetates that used a copper-pybox complex as the catalyst. However, the propargylation reaction in this particular case occurred at the *C*3-position of the indole instead of the *N*1-position. This result was consistent with the observation that the *C*3-position of indole is more reactive than its *N*1 and *C*2 positions towards the Friedel-Crafts alkylation reaction [22]. The development of an alternative strategy for the construction of optically active *N*-propargylindoles is therefore highly desirable.

In 2003, Corey's group [23] reported a strategy for the construction of *N*-propargylindole via the sequential *N*-propargylation and dehydrogenation of the corresponding indoline in their total synthesis of okaramines, which are a family of biologically active tryptophan-derived heptacyclic and octacyclic alkaloids that are produced by the fungus *Penicillium simplicissum* [24]. Although an asymmetric version of this reaction has never been reported, this strategy provided a platform for the enantioselective construction of optically active *N*-propargylindole. Employing a similar strategy, Liu et al. [25] recently

* Corresponding author. Tel: +86-411-84379276; Fax: +86-411-84684746; E-mail: xiangping@dicp.ac.cn
This work was supported by Dalian Institute of Chemical Physics, Chinese Academy of Sciences.
DOI: 10.1016/S1872-2067(14)60230-8 | http://www.sciencedirect.com/science/journal/18722067 | Chin. J. Catal., Vol. 36, No. 1, January 2015



Scheme 1. The enantioselective synthesis of *N*-propargylindoles via a sequential propargylic alkylation and dehydrogenation strategy.

developed a general process for the synthesis of *N*-allylindoles via the Ir-catalyzed allylic alkylation of indolines followed by an oxidation reaction. Compared with the Ir-catalyst used in this reaction, Cu salts are much cheaper and easier to handle, as well as being much less toxic. Herein, we wish to report the development of a highly enantioselective reaction for the Cu-catalyzed propargylic alkylation of indolines with propargylic esters, followed by dehydrogenation of the resulting *N*-substituted indolines with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 1). This method can be used to provide facile and efficient access to optically active *N*-substituted indoles, which are privileged structural motifs found in numerous natural products and biologically active compounds [26].

2. Experimental

2.1. General

All reactions were carried out under N_2 atmosphere. All of the solvents were purified by standard procedures before being used. Commercial reagents were used as supplied without further purification. Flash column chromatography (FCC) was performed over silica gel 60 (40–63 μm; Qingdao Makall Group Co., LTD, Qingdao, China). Thin layer chromatography (TLC) was performed on glass plates coated with silica gel 60 with an F254 indicator (Yantai Jiangyou Silica Gel Development Co., LTD, Yantai, China). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker 400 MHz spectrometer (Bruker, Switzerland). The chemical shifts (δ) of the protons have been reported in parts per million (ppm) downfield of tetramethylsilane, which was used as a reference together with the residual proton of the deuterated NMR solvent (i.e., $CHCl_3$ = δ 7.28). ^{13}C NMR spectra were recorded on a Bruker 101 MHz spectrometer. The chemical shifts (δ) for carbon signals have been reported in ppm downfield from tetramethylsilane, which was used as a reference together with the carbon resonances of the deuterated solvent (i.e., $CDCl_3$ = δ 77.07). NMR data have been presented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (J) in Hz and integration. Enantiomeric ratios were determined by chiral HPLC using *n*-hexane and *i*-PrOH as the mobile phases. Optical rotations were recorded on a JASCO P-1020 polarimeter (JASCO Corporation, Tokyo, Japan).

2.2. General procedure for the synthesis of optically active N-propargylindoles via a one-pot propargylation/ dehydrogenation process

$Cu(OAc)_2{\cdot}H_2O$ (3.0 mg, 0.015 mmol) and (*S*)-**L5** (7.8 mg, 0.0165 mmol) were added to anhydrous methanol (1 mL), and the resulting mixture was stirred at room temperature under N_2 atmosphere for 1 h. The solution was then cooled to 0 °C and treated with a solution of indoline **1** (0.33 mmol), propargylic ester **2** (0.3 mmol) and *i*-Pr_2NEt (62 μL, 0.36 mmol) in anhydrous methanol (2 mL). The resulting mixture was stirred at 0 °C for 5 h before being warmed to room temperature and passed over a short pad of silica. The silica pad was eluted with a mixture of hexanes and ethyl acetate to give the crude *N*-propargylindoline product, which was treated with a solution of DDQ (0.33 mmol) in CH_2Cl_2 (3 mL) at room temperature for 5 min to give the oxidized product as a crude mixture. The desired *N*-propargylindole product **3** was purified by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate.

(*R*)-1-(1-Phenylprop-2-yn-1-yl)-1*H*-indole (**3aa**). Obtained as a colorless oil in 90% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 100/1); 92% ee was determined by chiral HPLC (Chiralcel OJ-H, *n*-hexane/*i*-PrOH = 50/50, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 25.4 min, t_R (minor) = 19.9 min; $[\alpha]_D^{29}$ = 121.3 (*c* 0.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 1H), 7.35–7.25 (m, 7H), 7.18–7.09 (m, 2H), 6.55 (dd, *J* = 3.3, 0.6 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 2.67 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.5, 135.6, 129.2, 128.9, 128.5, 126.7, 126.5, 121.9, 121.2, 120.0, 110.0, 102.5, 80.1, 75.5, 51.6; HRMS calculated for $C_{17}H_{13}N$ $[M+H]^+$, M_r = 232.1126, found M_r = 232.1128.

(*R*)-1-(1-(2-Chlorophenyl)prop-2-yn-1-yl)-1*H*-indole (**3ab**). Obtained as a colorless oil in 79% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 70/1); 85% ee was determined by chiral HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 8.4 min, t_R (minor) = 7.7 min; $[\alpha]_D^{29}$ = 1.31 (*c* 0.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.61 (m, 1H), 7.41–7.09 (m, 8H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.56 (d, *J* = 3.3 Hz, 1H), 2.67 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.5, 135.2, 133.1, 130.0, 130.0, 129.2, 128.5, 127.5, 126.2, 122.0, 121.2, 120.2, 109.8, 102.4, 79.1, 75.8, 49.0; HRMS calculated for $C_{17}H_{12}ClN$ $[M+H]^+$, M_r = 266.0737, found M_r = 266.0735.

(*R*)-1-(1-(3-Chlorophenyl)prop-2-yn-1-yl)-1*H*-indole (**3ac**). Obtained as a colorless oil in 88% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 100/1); 93% ee was determined by chiral HPLC (Chiralcel OJ-H, *n*-hexane/*i*-PrOH = 50/50, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 17.3 min, t_R (minor) = 14.2 min; $[\alpha]_D^{29}$ = 145.9 (*c* 0.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.63 (m, 1H), 7.40 (d, *J* = 1.4 Hz, 1H), 7.30–7.10 (m, 7H), 6.58 (dd, *J* = 2.6, 2.2Hz, 1H), 6.35 (d, *J* = 1.9 Hz, 1H), 2.71 (dd, *J* = 2.5, 0.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.6, 135.5, 134.9, 130.1, 129.2, 128.7, 126.9,

126.3, 124.8, 122.1, 121.3, 120.2, 109.8, 102.9, 79.4, 76.1, 51.1; HRMS calculated for $C_{17}H_{12}ClN$ $[M+H]^+$, M_r = 266.0737, found M_r = 266.0733.

(*R*)-1-(1-(4-Chlorophenyl)prop-2-yn-1-yl)-1*H*-indole (**3ad**). Obtained as a colorless oil in 91% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 100/1); 91% ee was determined by chiral HPLC (Chiralcel OJ-H, *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 21.9 min, t_R (minor) = 20.3 min; $[\alpha]_D^{29}$ = 161.7 (*c* 0.58, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 1H), 7.28–7.09 (m, 8H), 6.56–6.55 (m, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 2.68 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.1, 135.5, 134.4, 129.3, 129.1, 128.1, 126.4, 122.1, 121.3, 120.2, 109.9, 102.8, 79.6, 75.9, 51.1; HRMS calculated for $C_{17}H_{12}ClN$ $[M+H]^+$, M_r = 266.0737, found M_r = 266.0733.

(*R*)-1-(1-(4-Bromophenyl)prop-2-yn-1-yl)-1*H*-indole (**3ae**). Obtained as a colorless oil in 92% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 100/1); 89% ee was determined by chiral HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 10.5 min, t_R (minor) = 17.0 min; $[\alpha]_D^{29}$ = 138.0 (*c* 0.70, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.27–7.11 (m, 6H), 6.56 (dd, *J* = 2.2, 1.0 Hz, 1H), 6.32 (d, *J* = 2.3 Hz, 1H), 2.68 (dd, *J* = 2.5, 0.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.6, 135.5, 132.0, 129.3, 128.4, 126.4, 122.6, 122.1, 121.3, 120.2, 109.9, 102.8, 79.5, 76.0, 51.1; HRMS calculated for $C_{17}H_{12}BrN$ $[M+H]^+$, M_r = 310.0231, found M_r = 310.0231.

(*R*)-1-(1-(4-(Trifluoromethyl)phenyl)prop-2-yn-1-yl)-1*H*-indole (**3af**). Obtained as a colorless oil in 86% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 100/1); 90% ee was determined by chiral HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 9.8 min, t_R (minor) = 14.2 min; $[\alpha]_D^{29}$ = 97.8 (*c* 0.56, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.56 (m, 3H), 7.42–7.11 (m, 6H), 6.60 (d, *J* = 3.3 Hz, 1H), 6.43 (d, *J* = 2.3 Hz, 1H), 2.73 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.5, 135.4, 130.8 (q, *J* = 32.5 Hz), 129.3, 127.0, 126.3, 125.9 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 272.1 Hz), 122.1, 121.4, 120.3, 109.8, 103.0, 79.2, 76.3, 51.3; HRMS calculated for $C_{18}H_{12}F_3N$ $[M+H]^+$, M_r = 300.1000, found M_r = 300.1003.

(*R*)-1-(1-(p-Tolyl)prop-2-yn-1-yl)-1*H*-indole (**3ag**). Obtained as a colorless oil in 87% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 100/1); 90% ee was determined by chiral HPLC (Chiralcel OJ-H, *n*-hexane/*i*-PrOH = 50/50, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 25.6 min, t_R (minor) = 17.0 min; $[\alpha]_D^{29}$ = 81.7 (c 0.45, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.61 (m, 1H), 7.35–7.09 (m, 8H), 6.54 (d, *J* = 3.3 Hz, 1H), 6.36 (d, *J* = 1.8 Hz, 1H), 2.66 (dd, *J* = 2.5, 0.9 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.3, 135.6, 134.5, 129.5, 129.2, 126.7, 126.4, 121.8, 121.1, 119.9, 110.0, 102.3, 80.3, 75.3, 51.4, 21.1; HRMS calculated for $C_{18}H_{15}N$ $[M+H]^+$, M_r = 246.1283, found M_r = 246.1281.

(*R*)-1-(1-(4-Methoxyphenyl)prop-2-yn-1-yl)-1*H*-indole (**3ah**). Obtained as a colorless oil in 85% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 70/1); 83% ee was determined by chiral HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 11.7 min, t_R (minor) = 19.9 min; $[\alpha]_D^{29}$ = 134.5 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.61 (m, 1H), 7.36–7.09 (m, 6H), 6.86–6.84 (m, 2H), 6.54 (d, *J* = 3.2 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 3.77 (s, 3H), 2.67 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.7, 135.5, 129.5, 129.2, 128.1, 126.3, 121.8, 121.2, 119.9, 114.2, 110.0, 102.3, 80.3, 75.2, 55.3, 51.1; HRMS calculated for $C_{18}H_{15}NO$ $[M+H]^+$, M_r = 262.1232, found M_r = 262.1229.

(*R*)-1-(1-(Naphthalen-2-yl)prop-2-yn-1-yl)-1*H*-indole (**3ai**). Obtained as a colorless oil in 88% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 70/1); 87% ee was determined by chiral HPLC (Chiralcel OJ-H, *n*-hexane/*i*-PrOH = 50/50, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 36.3 min, t_R (minor) = 26.9 min; $[\alpha]_D^{29}$ = 205.4 (*c* 0.46, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.63 (m, 5H), 7.48–7.09 (m, 7H), 6.57–6.54 (m, 2H), 2.73 (dd, *J* = 2.4, 1.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.7, 134.7, 133.2, 133.2, 129.3, 128.9, 128.3, 127.7, 126.6, 126.6, 126.5, 125.9, 124.4, 122.0, 121.2, 120.1, 110.0, 102.6, 80.0, 75.9, 51.8; HRMS calculated for $C_{21}H_{15}N$ $[M+H]^+$, M_r = 282.1283, found M_r = 282.1280.

(*R*)-1-(1-(Thiophen-2-yl)prop-2-yn-1-yl)-1*H*-indole (**3aj**). Obtained as a colorless oil in 89% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 100/1); 91% ee was determined by chiral HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 11.3 min, t_R (minor) = 19.4 min; $[\alpha]_D^{29}$ = 162.6 (*c* 0.14, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.29–7.08 (m, 5H), 6.90 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.56–6.54 (m, 2H), 2.67 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.0, 135.4, 129.3, 126.9, 126.4, 126.2, 126.0, 122.0, 121.3, 120.2, 109.9, 102.9, 79.6, 74.9, 47.5; HRMS calculated for $C_{15}H_{11}NS$ $[M+H]^+$, M_r = 238.0690, found M_r = 238.0689.

(*R*)-3-Methyl-1-(1-phenylprop-2-yn-1-yl)-1*H*-indole (**3ba**). Obtained as a colorless oil in 89% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 100/1); 94% ee was determined by chiral HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 10.1 min, t_R (minor) = 12.7 min; $[\alpha]_D^{29}$ = 116.4 (*c* 0.46, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.55 (m, 1H), 7.36–7.09 (m, 8H), 7.03 (s, 1H), 6.34 (s, 1H), 2.64 (dd, *J* = 2.4, 0.9 Hz, 1H), 2.32–2.31 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.7, 136.0, 129.5, 128.8, 128.4, 126.8, 123.9, 121.9, 119.4, 119.3, 111.8, 109.7, 80.4, 75.2, 51.3, 9.7; HRMS calculated for $C_{18}H_{15}N$ $[M+H]^+$, M_r = 246.1283, found M_r = 246.1281.

(*R*)-2-Methyl-1-(1-phenylprop-2-yn-1-yl)-1*H*-indole (**3ca**). Obtained as a yellow solid in 90% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 100/1); m.p. = 53–55 °C; 89% ee was de-

termined by chiral HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 7.8 min, t_R (minor) = 9.5 min; $[\alpha]_D^{29}$ = 208.5 (*c* 0.76, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.50 (m, 1H), 7.28–7.24 (m, 6H), 7.07–7.03 (m, 2H), 6.51 (s, 1H), 6.32 (s, 1H), 2.64 (dd, *J* = 2.4, 2.0 Hz, 1H), 2.38–2.37 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.2, 136.5, 136.3, 128.7, 128.6, 128.1, 126.3, 126.3, 120.8, 119.9, 110.6, 101.9, 79.7, 75.2, 48.9, 13.5; HRMS calculated for $C_{18}H_{15}N$ $[M+H]^+$, M_r = 246.1283, found M_r = 246.1279.

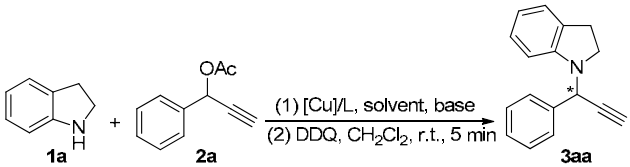
(*R*)-4-Methyl-1-(1-phenylprop-2-yn-1-yl)-1*H*-indole (**3da**). Obtained as a colorless oil in 86% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 100/1); 88% ee was determined by chiral HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 8.5 min, t_R (minor) = 10.4 min; $[\alpha]_D^{29}$ = 98.9 (*c* 0.50, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 6H), 7.20–7.05 (m, 2H), 6.92–6.90 (m, 1H), 6.58–6.57 (m, 1H), 6.38 (s, 1H), 2.66 (dd, *J* = 2.4, 2.0 Hz, 1H), 2.54 (d, *J* = 2.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.5, 135.4, 130.7, 129.0, 128.9, 128.4, 126.7, 125.8, 122.1, 120.3, 107.6, 101.0, 80.2, 75.5, 51.7, 18.7; HRMS calculated for $C_{18}H_{15}N$ $[M+H]^+$, M_r = 246.1283, found M_r = 246.1282.

(*R*)-6-Fluoro-1-(1-phenylprop-2-yn-1-yl)-1*H*-indole (**3ea**). Obtained as a colorless oil in 91% yield following purification by FCC over silica gel eluting with a mixture of hexanes and ethyl acetate (*V*/*V* = 100/1); 90% ee was determined by chiral HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5, 0.8 mL/min, detection at 230 nm, column temperature 40 °C): t_R (major) = 8.3 min, t_R (minor) = 9.2 min. $[\alpha]_D^{29}$ = 94.7 (*c* 0.80, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.50 (m, 1H), 7.33–7.23 (m, 6H), 7.01 (d, *J* = 9.9 Hz, 1H), 6.89–6.84 (m, 1H), 6.52 (d, *J* = 3.3 Hz, 1H), 6.28 (d, *J* = 2.4 Hz, 1H), 2.70 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.7 (d, *J* = 237.9 Hz), 137.0, 135.5 (d, *J* = 12.2 Hz), 128.9, 128.6, 127.0 (d, *J* = 3.7 Hz), 126.7, 125.6, 121.8 (d, *J* = 10.2 Hz), 108.8 (d, *J* = 24.6 Hz), 102.5, 96.8 (d, *J* = 26.8 Hz), 79.6, 75.9, 52.0; HRMS calculated for $C_{17}H_{12}FN$ $[M+H]^+$, M_r = 250.1032, found M_r = 250.1026.

3. Results and discussion

The optically active *N*-propargylindoles were prepared according to the strategy reported by Corey et al. [23] via an *N*-propargylation/dehydrogenation sequence (Scheme 1). The optical purity of the *N*-propargylindole products was found to be determined during the propargylic alkylation step. With this in mind, we screened a variety of chiral ligands in this reaction that have been proven to be performed effectively as ligands in various other Cu-catalyzed asymmetric propargylic substitution reactions [1,2,12,16]. Indoline (**1a**) and 1-phenylprop-2-yn-1-yl acetate (**2a**) were selected as model substrates for this reaction, which was performed in the presence of 5 mol% Cu catalyst (prepared in situ from 5 mol% $Cu(OAc)_2{\cdot}H_2O$ and 5.5 mol% chiral ligand) and 1.2 equiv of *i*-Pr_2NEt in MeOH (3 mL) at 0 °C for 5 h. Upon completion of the propargylation reaction, the Cu catalyst was removed by filtration. Evaporation of the MeOH solvent gave the crude *N*-propargylindoline as a residue, which was treated with a solution of DDQ in CH_2Cl_2 at room temperature to give the corresponding dehydrogenated product in only 5 min. The desired 1-(1-phenylprop-2-yn-1-yl)-1*H*-indole (**3aa**) was obtained in good yield in all cases, although it is noteworthy that the structure of the ligand was found to have a significant impact on the enantioselectivity of the reaction (Table 1, entries 1–5). For example, BINAP (**L1**) and the P,N,N-ligands **L3** and **L4** gave moderate enantioselectivity (Table 1, entries 1, 3, and 4), whereas the tridentate N-ligand **L2** gave a low enantioselectivity (Table 1, entry 2). The bulky and structurally rigid chiral tridentate ketimine P,N,N-ligand (*S*)-**L5**, which was developed in our group, gave the best result of all of the ligands screened in this reaction in terms of its reactivity

Table 1
Screening the reaction condition.



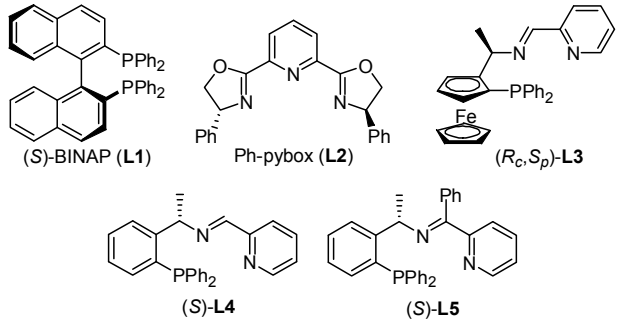
Entry	[Cu]	L	Base	Solvent	Yield [a] (%)	ee [b] (%)
1	$Cu(OAc)_2{\cdot}H_2O$	**L1**	*i*-Pr_2NEt	MeOH	87	72 (*R*)
2	$Cu(OAc)_2{\cdot}H_2O$	**L2**	*i*-Pr_2NEt	MeOH	87	38 (*S*)
3	$Cu(OAc)_2{\cdot}H_2O$	**L3**	*i*-Pr_2NEt	MeOH	85	79 (*S*)
4	$Cu(OAc)_2{\cdot}H_2O$	**L4**	*i*-Pr_2NEt	MeOH	89	76 (*R*)
5	$Cu(OAc)_2{\cdot}H_2O$	**L5**	*i*-Pr_2NEt	MeOH	90	92 (*R*)
6	$Cu(OTf)_2$	**L5**	*i*-Pr_2NEt	MeOH	89	92 (*R*)
7	CuCl	**L5**	*i*-Pr_2NEt	MeOH	81	87 (*R*)
8	CuI	**L5**	*i*-Pr_2NEt	MeOH	82	83 (*R*)
9	$Cu(CH_3CN)_4BF_4$	**L5**	*i*-Pr_2NEt	MeOH	87	91 (*R*)
10	$Cu(OAc)_2{\cdot}H_2O$	**L5**	DBU	MeOH	65	76 (*R*)
11	$Cu(OAc)_2{\cdot}H_2O$	**L5**	Et_3N	MeOH	88	92 (*R*)
12	$Cu(OAc)_2{\cdot}H_2O$	**L5**	—	MeOH	45	25 (*R*)
13	$Cu(OAc)_2{\cdot}H_2O$	**L5**	K_2CO_3	MeOH	88	89 (*R*)
14	$Cu(OAc)_2{\cdot}H_2O$	**L5**	*i*-Pr_2NEt	CH_2Cl_2	—	—
15	$Cu(OAc)_2{\cdot}H_2O$	**L5**	*i*-Pr_2NEt	Toluene	—	—
16	$Cu(OAc)_2{\cdot}H_2O$	**L5**	*i*-Pr_2NEt	THF	—	—
17	$Cu(OAc)_2{\cdot}H_2O$	**L5**	*i*-Pr_2NEt	DMF	—	—
18	$Cu(OAc)_2{\cdot}H_2O$	**L5**	*i*-Pr_2NEt	DMSO	—	—
19	$Cu(OAc)_2{\cdot}H_2O$	**L5**	*i*-Pr_2NEt	MeOH	35	92 (*R*) [c]

Reaction conditions: (1) **1a** (0.33 mmol), **2a** (0.3 mmol), [Cu] (0.015 mmol, 5 mol%), L (0.0165 mmol, 5.5 mol%) and base (0.36 mmol) in solvent (3 mL) at 0 °C for 5 h; (2) DDQ (0.33 mmol) in CH_2Cl_2 (3 mL) at r.t. for 5 min.

[a] Isolated yield.

[b] Determined by chiral HPLC analysis.

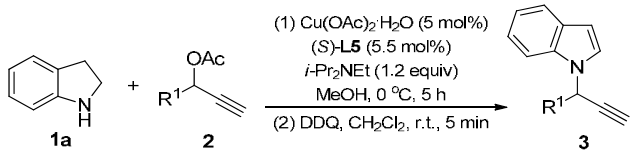
[c] A solution of DDQ in CH_2Cl_2 (3 mL) was added directly to the reaction mixture following the removal of MeOH under reduced pressure.



and enantioselectivity, and was selected as the optimum ligand for further evaluation (Table 1, entry 5).

A variety of different Cu sources were also screened in this model reaction, but the results revealed that the type of Cu salts used in the transformation had no discernible impact on the reactivity or enantioselectivity of the reaction (Table 1, entries 5–9). These results demonstrated that $Cu(OAc)_2·H_2O$ was the best source of Cu for the reaction (Table 1, entry 5). The addition of a base was determined to be critical to the success of this reaction, with the product being formed in a very low yield and enantioselectivity when the reaction was performed in the absence of base (Table 1, entry 12). The addition of a stronger base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), had a detrimental impact on the yield and enantioselectivity of the reaction (Table 1, entry 10), whereas the use of Et_3N provided similar good result to that of *i*-Pr_2NEt (Table 1, entry 11). Interestingly, the inorganic base K_2CO_3 also performed efficiently in the reaction, with the desired product being formed in good yield and enantioselectivity (Table 1, entry 13). The effect of the solvent on the outcome of the model reaction was also investigated, and the results revealed a significant solvent dependency. For example, MeOH was found to be the only one of the six different solvents tested to be suitable for the transformation, with very little product being observed when the reaction was conducted in CH_2Cl_2, toluene, tetrahydrofuran, *N*,*N*-dimethylformamide or dimethyl sulfoxide (Table 1, entries 14–18). These results were found to be consistent with those observed in other Cu-catalyzed asymmetric propargylic substitution reactions [1,2]. Pleasingly, a one-pot version of this reaction also worked well, with 1.1 equivalents of DDQ being added directly to the reaction mixture upon the completion of Cu-catalyzed propargylic amination step. Disappointingly, however, this process gave a much lower yield of the desired product, albeit with a high enantioselectivity (Table 1, entry 19). This result suggested that the Cu salt had an adverse impact on the DDQ-mediated dehydrogenation process.

Table 2
Cu-catalyzed propargylation/dehydrogenation of indoline (**1a**) with propargylic esters (**2**).



1a **2** **3**

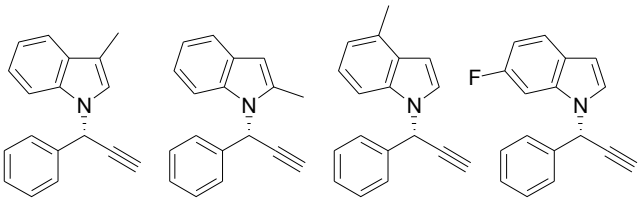
Entry	**2** (R^1)	**3**	Yield [a] (%)	ee [b] (%)
1	**2a**: R^1 = Ph	**3aa**	90	92 (*R*) [c]
2	**2b**: R^1 = 2-ClC_6H_4	**3ab**	79	85
3	**2c**: R^1 = 3-ClC_6H_4	**3ac**	88	93
4	**2d**: R^1 = 4-ClC_6H_4	**3ad**	91	91
5	**2e**: R^1 = 4-BrC_6H_4	**3ae**	92	89
6	**2f**: R^1 = 4-$CF_3C_6H_4$	**3af**	86	90
7	**2g**: R^1 = 4-MeC_6H_4	**3ag**	87	90
8	**2h**: R^1 = 4-$MeOC_6H_4$	**3ah**	85	83
9	**2i**: R^1 = 2-naphthyl	**3ai**	88	87
10	**2j**: R^1 = 2-thienyl	**3aj**	89	91

Reaction conditions: (1) **1a** (0.33 mmol), **2** (0.3 mmol), $Cu(OAc)_2·H_2O$ (0.015 mmol, 5 mol%), (*S*)-**L5** (0.0165 mmol, 5.5 mol%) and *i*-Pr_2NEt (0.36 mmol) in MeOH (3 mL) at 0 °C for 5 h; (2) DDQ (0.33 mmol) in CH_2Cl_2 (3 mL) at r.t. for 5 min.

[a] Isolated yields.

[b] Determined by chiral HPLC analysis.

[c] The absolute configuration was determined by comparing the specific rotation of the corresponding 1-(1-phenylprop-2-yn-1-yl)indoline compound with the data reported in Ref. [8].



3ba 89% yield, 94% ee **3ca** 90% yield, 89% ee **3da** 86% yield, 88% ee **3ea** 91% yield, 90% ee

Fig. 1. Scope of indolines.

With optimized conditions in hand, we proceeded to investigate the scope of the reaction using a variety of different propargylic esters (Table 2). The results of the reactions indicated that the substitution pattern of the phenyl ring had an impact on the outcome of the reaction (Table 2, entries 2–4). For example, the 3- and 4-Cl substituted substrates (**2c** and **2d**, respectively) provided the corresponding indole products in good yields and high enantioselectivities (Table 2, entries 3 and 4), whereas the 2-Cl substituted substrate **2b** gave the corresponding product with a decreased yield and lower enantioselectivity (Table 2, entry 2). The electronic properties of the substituent at the para position of the phenyl ring also had a significant impact on the performance of the reaction. In most cases, the reaction gave good results, although the 4-MeO-substituted substrate **2h** gave a slight decrease in the enantioselectivity of the product to 83% ee (Table 2, entry 8). The 2-naphthyl substrate **2i** reacted smoothly to give 1-(1-(naphthalen-2-yl)prop-2-yn-1-yl)-1*H*-indole (**3ai**) in 88% yield and 87% ee (Table 2, entry 9). The 2-thienyl substrate **2j** also performed well in the reaction, with the corresponding *N*-propargylindole product **3aj** being formed in 89% yield and 91% ee (Table 2, entry 10).

The scope of the indolines was also evaluated (Fig. 1), and the results revealed that the optimized reaction could be successfully applied to a variety of substituted indolines. For example, 2-, 3- and 4-methyl indolines all reacted smoothly under the optimized conditions to give the corresponding *N*-propargylated indoles **3ba**, **3ca**, and **3da**, respectively, in good yields and high enantioselectivities. Electron-withdrawing substituents were also well tolerated on the indoline ring with 6-fluoroindoline reacting smoothly to give the *N*-propargylated fluoroindole product **3ea** in a high yield and enantioselectivity.

4. Conclusions

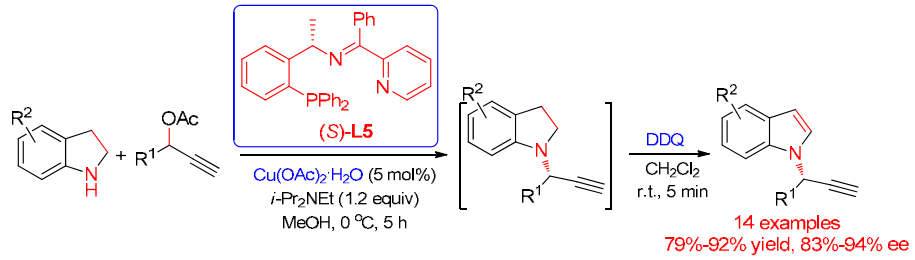
We have developed an efficient and highly enantioselective process for the construction of optically active *N*-propargylindoles via the Cu-catalyzed asymmetric propargylic amination of indolines with propargylic esters followed by the dehydrogenation of the resulting *N*-substituted indolines with DDQ. This reaction can be performed under mild conditions using a

Graphical Abstract

Chin. J. Catal., 2015, 36: 86–92 doi: 10.1016/S1872-2067(14)60230-8

Enantioselective *N*-propargylation of indoles via Cu-catalyzed propargylic alkylation/dehydrogenation of indolines

Fulin Zhu, Xiangping Hu*
Dalian Institute of Chemical Physics, Chinese Academy of Sciences; University of Chinese Academy of Sciences



A new strategy has been developed for the sequential Cu-catalyzed asymmetric propargylic alkylation and DDQ-mediated dehydrogenation of indolines using a bulky and structurally rigid ketimine P,N,N-ligand. This reaction allowed for the enantioselective synthesis of optically active *N*-propargylindoles.

broad range of different substrates, with the resulting chiral *N*-propargylindole products being formed in good yields and high enantioselectivities. Further work towards the development and application of this reaction is currently underway in our laboratory.

References

[1] Hattori G, Matsuzawa H, Miyake Y, Nishibayashi Y. *Angew Chem Int Ed*, 2008, 47: 3781
[2] Detz R J, Delville M M E, Hiemstra H, van Maarseveen J H. *Angew Chem Int Ed*, 2008, 47: 3777
[3] Nishibayashi Y. *Synthesis*, 2012, 44: 489
[4] Ding C H, Hou X L. *Chem Rev*, 2011, 111: 1914
[5] Fang P, Hou X L. *Org Lett*, 2009, 11: 4612
[6] Hattori G, Yoshida A, Miyake Y, Nishibayashi Y. *J Org Chem*, 2009, 74: 7603
[7] Hattori G, Miyake Y, Nishibayashi Y. *ChemCatChem*, 2010, 2: 155
[8] Hattori G, Sakata K, Matsuzawa H, Tanabe Y, Miyake Y, Nishibayashi Y. *J Am Chem Soc*, 2010, 132: 10592
[9] Detz R J, Abiri Z, le Griel R, Hiemstra H, van Maarseveen J H. *Chem Eur J*, 2011, 17: 5921
[10] Yoshida A, Ikeda M, Hattori G, Miyake Y, Nishibayashi Y. *Org Lett*, 2011, 13: 592
[11] Yoshida A, Hattori G, Miyake Y, Nishibayashi Y. *Org Lett*, 2011, 13: 2460
[12] Zhang C, Wang Y H, Hu X H, Zheng Z, Xu J, Hu X P. *Adv Synth Catal*, 2012, 354: 2854
[13] Zhang C, Hu X H, Wang Y H, Zheng Z, Xu J, Hu X P. *J Am Chem Soc*, 2012, 134: 9585
[14] Mino T, Taguchi H, Hashimoto M, Sakamoto M. *Tetrahedron: Asymmetry*, 2013, 24: 1520
[15] Han F Z, Zhu F L, Wang Y H, Zou Y, Hu X H, Chen S, Hu X P. *Org Lett*, 2014, 16: 588
[16] Zhu F L, Zou Y, Zhang D Y, Wang Y H, Hu X H, Chen S, Xu J, Hu X P. *Angew Chem Int Ed*, 2014, 53: 1410
[17] Zou Y, Zhu F L, Duan Z C, Wang Y H, Zhang D Y, Cao Z, Zheng Z, Hu X P. *Tetrahedron Lett*, 2014, 55: 2033
[18] Shibata M, Nakajima K, Nishibayashi Y. *Chem Commun*, 2014, 50: 7874
[19] Zhu F L, Wang Y H, Zhang D Y, Hu X H, Chen S, Hou C J, Xu J, Hu X P. *Adv Synth Catal*, 2014, 356: 3231
[20] Zhu F L, Wang Y H, Zhang D Y, Xu J, Hu X P. *Angew Chem Int Ed*, 2014, 53: 10223
[21] Zhang D Y, Zhu F L, Wang Y H, Hu X H, Chen S, Hou C J, Hu X P. *Chem Commun*, 2014, 50: 14459
[22] Bandini M, Umani-Ronchi A. Catalytic Asymmetric Friedel-Crafts Alkylations. Weinheim: Wiley-VCH, 2009
[23] Baran P S, Guerrero C A, Corey E J. *J Am Chem Soc*, 2003, 125: 5628
[24] Hayashi H, Takiuchi K, Murao S, Arai M. *Agric Biol Chem*, 1989, 53: 461
[25] Liu W B, Zhang X, Dai L X, You S L. *Angew Chem Int Ed*, 2012, 51: 5183
[26] Galm U, Hager M H, van Lanen S G, Ju J H, Thorson J S, Shen B. *Chem Rev*, 2005, 105: 739

Page numbers refer to the contents in the print version, which include both the English and Chinese versions of the paper. The online version only has the English version. The pages with the Chinese version are only available in the print version.