Ruthenium-Catalyzed Enantioselective Propargylation of Indoles with Propargylic Alcohols

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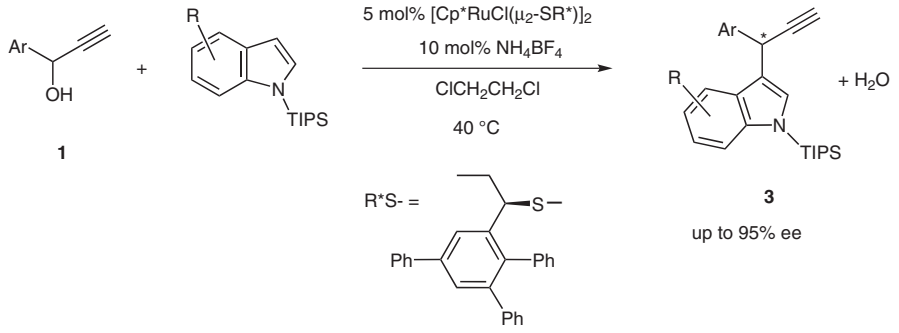
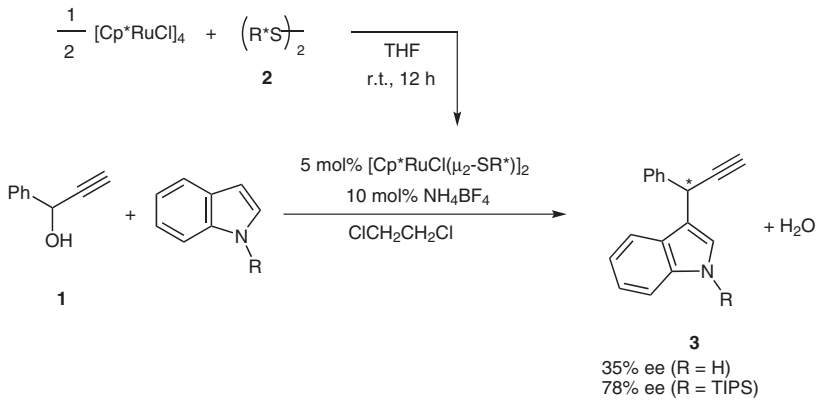
Abstract: Ruthenium-catalyzed enantioselective propargylation of 1-(triisopropylsilyl)-1*H*-indoles with propargylic alcohols gives the corresponding β-propargylated indoles in good yields with high enantioselectivity. Reactions with 1-(1-naphthyl)prop-2-yn-1-ol achieve the highest enantioselectivity (up to 95% ee).

Key words: asymmetric synthesis, Friedel–Crafts alkylation, ruthenium, indoles, propargylic alcohols



Scheme 1

Indoles represent a structural motif in a number of natural bioactive products. A variety of methods to obtain optically active indoles have been reported by Lewis acid and Brønsted acid catalyzed enantioselective Friedel–Crafts alkylation of indoles.[1,2] We have recently disclosed the enantioselective propargylation of aromatic compounds such as 2-alkylfurans and *N*,*N*-dimethylaniline with propargylic alcohols catalyzed by a chiral thiolate-bridged diruthenium complex[3] to afford the corresponding propargylated products in good yields with high enantioselectivity (up to 94% ee).[4] This is the first example of the enantioselective propargylation of aromatic compounds. As an extension of our study, we have more recently found the ruthenium-catalyzed enantioselective propargylation of indoles with propargylic alcohols to give the corresponding β-propargylated indoles in good to high yields (Scheme 1).[5] In this reaction system, the introduction of a bulky group, such as the triisopropylsilyl (TIPS) moiety,



Scheme 2 The remarkable effect of the N-substituent on the enantioselective propargylation of indoles

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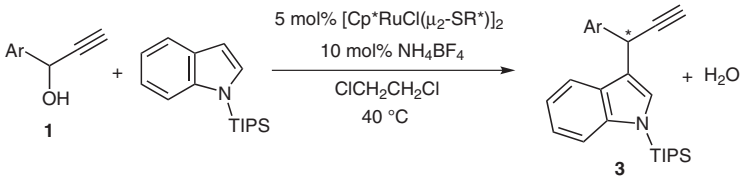
Table 1 Ruthenium-Catalyzed Enantioselective Propargylation of 1-(Triisopropylsilyl)-1*H*-indole with Propargylic Alcohols **1**[a]

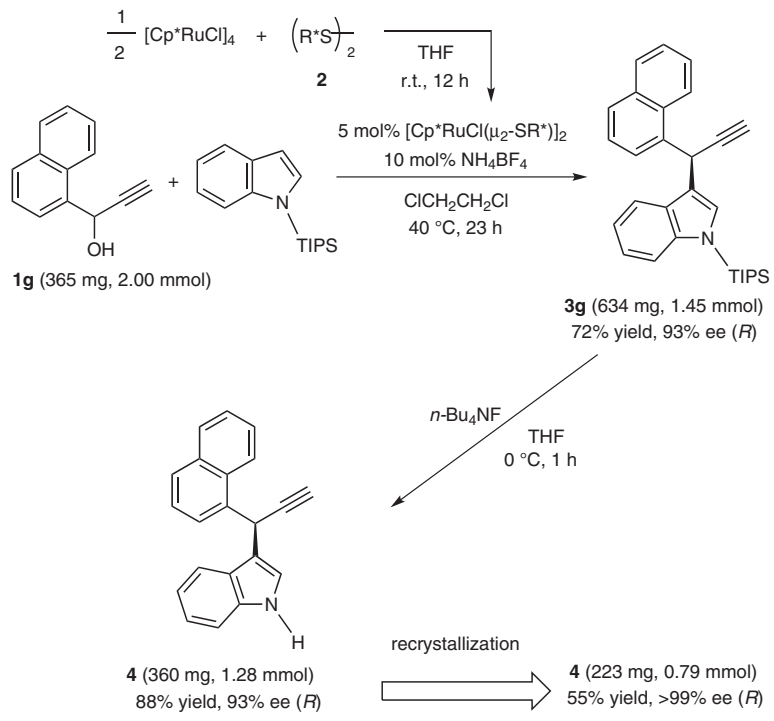


Entry	Ar of **1**	Time (h)	Yield[b] (%)	ee[c] (%)
1	Ph (**1a**)	7	**3a**, 77	78
2	4-MeC_6H_4 (**1b**)	10	**3b**, 70	71
3	4-ClC_6H_4 (**1c**)	7	**3c**, 72	79
4	4-PhC_6H_4 (**1d**)	10	**3d**, 76	90
5	2-PhC_6H_4 (**1e**)	30	**3e**, 63	83
6	3,5-$Ph_2C_6H_3$ (**1f**)	7	**3f**, 98	80
7	1-naphthyl (**1g**)	23	**3g**, 81	92
8	2-naphthyl (**1h**)	7	**3h**, 82	84

[a] Reaction conditions: **1a**–**h** (0.20 mmol), 1-(triisopropylsilyl)-1*H*-indole (0.60 mmol), ruthenium complex (0.010 mmol, generated in situ from $[Cp^*RuCl]_4$ and **2**), NH_4BF_4 (0.020 mmol), DCE (5 mL).
[b] Isolated yield of **3**.
[c] Determined by HPLC.

at the nitrogen of indole dramatically increased the enantioselectivity of the propargylated indoles (Scheme 2).[5] Herein, we describe a practical method for the preparation of β-propargylated indoles from reactions of 1-(triisopropylsilyl)-1*H*-indole with propargylic alcohols catalyzed by a chiral thiolate-bridged diruthenium complex.

As described in our previous paper, we have already found that the highest enantioselectivity was observed when 1-(1-naphthyl)prop-2-yn-1-ol (**1g**) was used as a substrate.[5] Typical results are shown in Table 1. In fact, the reaction of 1-(1-naphthyl)prop-2-yn-1-ol (**1g**) with 1-(triisopropylsilyl)-1*H*-indole (3 equiv) in 1,2-dichloroethane in the presence of a catalytic amount of a chiral thi-



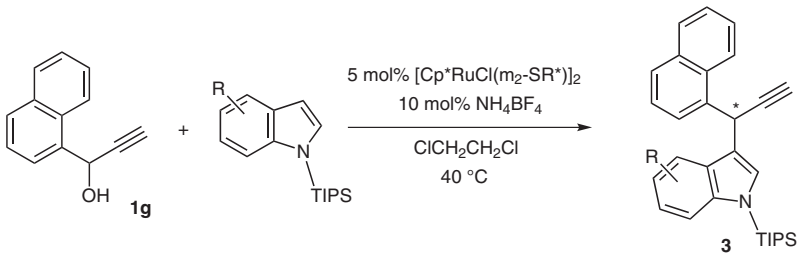
Scheme 3 A large-scale reaction of 1-(1-naphthyl)prop-2-yn-1-ol (**1g**) with 1-(triisopropylsilyl)-1*H*-indole

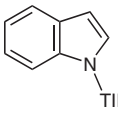
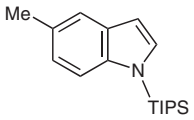
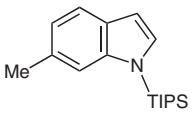
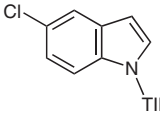
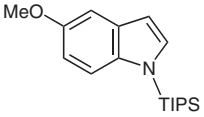
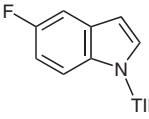
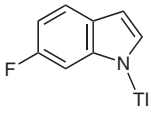
olate-bridged diruthenium complex, which was prepared in situ from the tetranuclear ruthenium(II) complex $[Cp^*RuCl]_4$ and chiral disulfide **2**[3] in tetrahydrofuran at room temperature for 12 hours, and ammonium tetrafluoroborate at 40 °C for 23 hours afforded 3-[1-(1-naphthyl)prop-2-ynyl]-1-(triisopropylsilyl)-1*H*-indole (**3g**) in 72% isolated yield with 93% ee (*R*)[5] (Scheme 3). After recrystallization of the deprotected indole, enantiomerically pure β-propargylated indole **4** was obtained in 55% isolated yield.

Next, the propargylation of other 1-(triisopropylsilyl)-1*H*-indoles bearing a substituent in the 5- or 6-position of the indole ring with **1g** was carried out under the same reaction conditions. Typical results are shown in Table 2. The introduction of a methyl group at the 5- or 6-position of the indole ring gave a similar enantioselectivity (Table 2, entries 2 and 3). The same enantioselectivity was observed when a chloro moiety is presented at 5-position of the indole ring (Table 2, entry 4). On the other hand, the introduction of methoxy or fluoro moiety at the 5- or 6-position of the indole ring gave a slightly lower enantioselectivity (Table 2, entries 5–7).

In summary, we have developed an efficient and practical method for the preparation of β-propargylated indoles from reactions of 1-(triisopropylsilyl)-1*H*-indole with propargylic alcohols catalyzed by a chiral thiolate-bridged diruthenium complex. This method provides a novel protocol for the asymmetric Friedel–Crafts alkyla-

Table 2 Ruthenium-Catalyzed Enantioselective Propargylation of 1-(Triisopropylsilyl)-1*H*-indoles with **1g**[a]



Entry	Indole	Time (h)	Yield[b] (%)	ee[c] (%)
1		23	**3g**, 81	93
2		20	**3i**, 82	95
3		24	**3j**, 83	92
4		20	**3k**, 78	91
5		20	**3l**, 71	87
6		48	**3m**, 51	80
7		24	**3n**, 78	81

[a] Reaction conditions: **1g** (0.20 mmol), 1-(triisopropylsilyl)-1*H*-indoles (0.60 mmol), ruthenium complex (0.010 mmol, generated in situ from $[Cp^*RuCl]_4$ and **2**), NH_4BF_4 (0.020 mmol), DCE (5 mL).
[b] Isolated yield of **3**.
[c] Determined by HPLC.

tion of indoles by using propargylic alcohols as a new type of electrophile.

^{1}H NMR (270 MHz) and ^{13}C NMR (67.8 MHz) spectra were measured on a Jeol Excalibur 270 spectrometer using $CDCl_3$ as solvent. HPLC analyses were performed on a Hitachi L-7100 apparatus equipped with a UV detector using 25 cm × 4.6 mm Daicel Chiralcel OD and Chiralpak IA columns. Mass spectra were measured on a Jeol JMS-700 mass spectrometer.

All reactions were carried out under a dry N_2 atmosphere. Chiral disulfide **2** was prepared according to our previous procedure.[3] 1-Phenylprop-2-yn-1-ol (**1a**) is commercially available. Preparation of other propargylic alcohols was carried out according to literature methods.[6] 1-(Triisopropylsilyl)-1*H*-indole was prepared according to the literature method.[7] DCE and THF were distilled under N_2 over P_2O_5 and Na benzophenone ketyl, respectively, and degassed. All products were fully characterized.[5]

3-[1-(1-Naphthyl)prop-2-ynyl]-1-(triisopropylsilyl)-1*H*-indole (3g); Typical Procedure

In a 200-mL round-bottomed flask were placed [Cp*RuCl]$_4$ (55.3 mg, 0.05 mmol) and bis[(*R*)-1-(6′-phenyl-1,1′:4′,1″-terphenyl-2′-yl)propyl] disulfide (**2**, 76.4 mg, 0.10 mmol) under N_2. Anhyd THF (10 mL) was added and the mixture was magnetically stirred at r.t. for 12 h. The solvent was evaporated in vacuo. Then, NH_4BF_4 (21.8 mg, 0.20 mmol) and anhyd DCE (50 mL) were added under N_2, and the mixture was magnetically stirred at r.t. After the addition of **1g** (365 mg, 2.0 mmol) and 1-(triisopropylsilyl)-1*H*-indole (1.64 g, 6.0 mmol), the reaction flask was kept at 40 °C for 23 h. The solvent was concentrated under reduced pressure by an aspirator, and then the residue was purified by flash column chromatography (silica gel, hexane–EtOAc; hexane only to 100:1) to give **3g** (634 mg, 72%) as a pale yellow oil; 93% ee [HPLC (Daicel Chiralpak IA, hexane–*i*-PrOH, 99:1, flow rate = 0.5 mL/min, λ = 254 nm): t_R = 11.6 (major), 14.0 min (minor)].

3-[1-(1-Naphthyl)prop-2-ynyl]-1*H*-indole (4)

In a 20-mL round-bottomed flask was placed **3g** (634 mg, 1.45 mmol) under N_2. Anhyd THF (7.5 mL) was added and the mixture was cooled to 0 °C. Then, 1 M TBAF in THF (2.9 mL, 2.9 mmol) was added dropwise to the mixture and the mixture was magnetically stirred at 0 °C for 1 h. CH_2Cl_2 (20 mL) was added and the organic layer was washed with H_2O (3 × 20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried (anhyd $MgSO_4$). The solvent was concentrated under reduced pressure by an aspirator, and the residue was purified by flash column chromatography (silica gel, hexane–EtOAc, 10:1) to give **4**[5] (360 mg, 88%) as a white solid; 93% ee. The product was further purified by recrystallization (hexane–EtOAc) to give enantiomerically pure **4** (223 mg, 55%); >99% ee [HPLC (Daicel Chiralpak IA, hexane–*i*-PrOH, 9:1, flow rate = 1.0 mL/min, l = 254 nm): t_R = 15.1 (major), 16.5 min (minor)].

$[\alpha]_D^{27}$ –6.3 (*c* 1.10, $CHCl_3$).

6-Methyl-3-[1-(1-naphthyl)prop-2-ynyl]-1-(triisopropylsilyl)-1*H*-indole (3j)

Brown oil; yield: 83%; 92% ee [HPLC (Daicel Chiralpak OD, hexane–*i*-PrOH, 49:1, flow rate = 0.5 mL/min, λ = 254 nm): t_R = 13.7 (minor), 18.0 min (major)].

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.08 (dd, *J* = 5.1, 7.6 Hz, 18 H), 1.55–1.66 (m, 3 H), 2.42–2.44 (br, 4 H), 5.89 (s, 1 H), 6.84 (d, *J* = 7.9 Hz, 1 H), 7.02 (s, 1 H), 7.19–7.44 (m, 5 H), 7.56 (d, *J* = 7.1 Hz, 1 H), 7.75 (d, *J* = 8.2 Hz, 1 H), 7.82–7.86 (m, 1 H), 8.22–8.26 (m, 1 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 12.8, 18.0, 22.0, 32.0, 71.5, 84.7, 114.0, 116.6, 118.9, 121.2, 124.1, 125.4, 125.5, 125.6, 125.8, 127.4, 127.8, 128.7, 130.0, 131.1, 131.2, 134.0, 135.9, 142.2.

HRMS (EI): *m*/*z* [M] calcd for $C_{31}H_{37}NSi$: 451.2695; found: 451.2688.

5-Fluoro-3-[1-(1-naphthyl)prop-2-ynyl]-1-(triisopropylsilyl)-1*H*-indole (3m)

Brown oil; yield: 51%; 80% ee [HPLC (Daicel Chiralpak OD, hexane–*i*-PrOH, 49:1, flow rate = 0.5 mL/min, λ = 254 nm): t_R = 12.4 (minor), 16.9 min (major)].

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.06 (dd, *J* = 4.9, 7.5 Hz, 18 H), 1.52–1.63 (m, 3 H), 2.47 (d, *J* = 2.4 Hz, 1 H), 5.85 (d, *J* = 2.4 Hz, 1 H), 6.85 (dt, *J* = 2.6, 9.1 Hz, 1 H), 7.07–7.12 (m, 2 H), 7.34–7.47 (m, 4 H), 7.59 (d, *J* = 6.9 Hz, 1 H), 7.78 (d, *J* = 8.2 Hz, 1 H), 7.84–7.87 (m, 1 H), 8.18–8.22 (m, 1 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 12.7, 17.9, 32.1, 71.8, 84.3, 104.4 (d, $J_{C\text{-}F}$ = 24 Hz), 109.8 (d, $J_{C\text{-}F}$ = 26 Hz), 114.5 (d, $J_{C\text{-}F}$ = 10 Hz), 116.9 (d, $J_{C\text{-}F}$ = 5 Hz), 124.0, 125.4, 125.5, 125.8, 125.9, 128.1, 128.8, 130.1 (d, $J_{C\text{-}F}$ = 10 Hz), 131.1, 132.3, 134.1, 135.4, 138.1, 157.6 (d, $J_{C\text{-}F}$ = 235 Hz).

HRMS (EI): *m*/*z* [M] calcd for $C_{30}H_{34}FNSi$: 455.2445; found: 455.2460.

6-Fluoro-3-[1-(1-naphthyl)prop-2-ynyl]-1-(triisopropylsilyl)-1*H*-indole (3n)

Yellow oil; yield: 78%; 81% ee [HPLC (Daicel Chiralpak OD, hexane–*i*-PrOH, 49:1, flow rate = 0.5 mL/min, λ = 254 nm): t_R = 12.9 (minor), 18.6 min (major)].

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (dd, *J* = 5.1, 7.6 Hz, 18 H), 1.52–1.64 (m, 3 H), 2.45 (d, *J* = 2.5 Hz, 1 H), 5.88 (d, *J* = 2.5 Hz, 1 H), 6.78 (dt, *J* = 2.2, 9.1 Hz, 1 H), 7.03 (s, 1 H), 7.15 (dd, *J* = 2.2, 11.0 Hz, 1 H), 7.29–7.46 (m, 4 H), 7.56 (d, *J* = 7.1 Hz, 1 H), 7.77 (d, *J* = 8.2 Hz, 1 H), 7.84–7.87 (m, 1 H), 8.20–8.23 (m, 1 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 12.6, 18.0, 32.0, 71.7, 84.4, 100.4 (d, $J_{C\text{-}F}$ = 26 Hz), 108.2 (d, $J_{C\text{-}F}$ = 24 Hz), 116.9, 119.8 (d, $J_{C\text{-}F}$ = 10 Hz), 124.0, 125.4, 125.5, 125.8, 125.9, 126.1, 128.0, 128.8, 130.8 (d, $J_{C\text{-}F}$ = 4 Hz), 131.1, 134.0, 135.6, 141.7 (d, $J_{C\text{-}F}$ = 12 Hz), 159.7 (d, $J_{C\text{-}F}$ = 237 Hz).

HRMS (EI): *m*/*z* [M] calcd for $C_{30}H_{34}FNSi$: 455.2445; found: 455.2451.

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