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SILVER-CATALYZED SYNTHESIS OF 1,2-DIHYDROISOQUINOLINES THROUGH DIRECT ADDITION OF CARBON PRONUCLEOPHILES TO *ORTHO*-ALKYNYLARYL ALDIMINES

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Abstract – AgOTf-catalyzed reaction of *ortho*-alkynyl-arylaldimines with various kinds of pronucleophiles afforded a variety of 1,2-dihydroisoquinoline derivatives in good to high yields. Treatment of *ortho*-alkynyl-arylaldimines with a stoichiometric amount of AgOTf, followed by the protonation with TfOH produced isoquinolinium trifluoromethanesulfonate, which suggested the formation of isoquinolinium intermediate in the present direct addition reaction.

INTRODUCTION

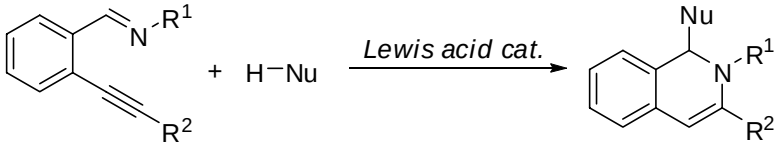
Metal-catalyzed addition of carbon nucleophiles to imines provide attractive and efficient methods for the preparation of nitrogen-containing organic compounds.[1] Particularly, the direct addition of carbon pronucleophiles to imines in the presence of catalysts is a highly desirable approach due to its atom-economical property.[2] Previously, we reported the first example of the transition metal-catalyzed direct addition of several carbon pronucleophiles, such as malononitrile and acetone, to activated imines.[3] Based on these results, we have recently communicated a silver-catalyzed preparation method of 1,2-dihydroisoquinoline derivatives through direct addition of carbon pronucleophiles to *ortho*-alkynyl-arylaldimines.[4] Now, we report the detailed study of the process including a diastereoselective formation of 1,2-dihydroisoquinolines.[5-7]

This paper is dedicated to Prof. Dr. Ryoji Noyori on the occasion of his 70th birthday.

RESULTS AND DISCUSSION

We examined the reaction of **1** with carbon pronucleophiles in the presence of Lewis acid catalysts and the results are summarized in Table 1. Treatment of **1a** ($R^1 = R^2 = Ph$) with nitromethane (2 equiv) in the presence of AgOTf (3 mol %) in $(CH_2Cl)_2$ at 80 °C for 1.5 h gave 1-nitromethyl-2,3-diphenyl-1,2-dihydro-isoquinoline (**2a**) in 85% yield (entry 1). On the other hand, the reaction of benzylidene phenylamine, bearing no alkynyl group at the proximal position, under similar conditions did not give the corresponding addition product, and the starting material was recovered in 81% yield. This result clearly showed that the *ortho*-alkynyl group of **1a** is essential for the present direct addition of nitromethane to the imine moiety. Besides AgOTf, $Cu(OTf)_2$ was a suitable catalyst for the present reaction while the AuCl-catalyzed reaction gave **2a** in only 1% yield (entries 2-3). The direct additions of nitromethane were also observed with other starting materials **1b-e**, and the corresponding products **2b-e** were obtained in moderate to high yields (entries 4-7). The reaction of **1a** with nitroethane gave **2f** as a mixture of diastereomers. The ratio was found to be 84:16 though the stereochemistry was not determined (entry 8). The reaction of **1a** with other pronucleophiles bearing activated methylene groups, such as acetylacetone, dimethyl malonate, and malononitrile, proceeded smoothly and the corresponding dihydroisoquinoline

Table 1. Direct addition of carbon pronucleophiles to **1**.[a]



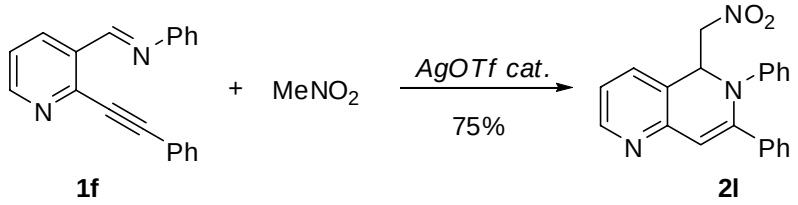
1 **2**

Entry	**1**	R^1	R^2	Lewis acid	Nu-H	**2**	Yield (%)[b]
1	**1a**	Ph	Ph	AgOTf	$MeNO_2$	**2a**	85
2	**1a**	Ph	Ph	$Cu(OTf)_2$	$MeNO_2$	**2a**	79
3	**1a**	Ph	Ph	AuCl	$MeNO_2$	**2a**	1
4[c]	**1b**	Bu	Ph	AgOTf	$MeNO_2$	**2b**	56
5	**1c**	Bn	Ph	AgOTf	$MeNO_2$	**2c**	58
6	**1d**	Ph	Bu	AgOTf	$MeNO_2$	**2d**	72
7	**1e**	Ph	1-cC_6H_9	AgOTf	$MeNO_2$	**2e**	80
8	**1a**	Ph	Ph	AgOTf	$EtNO_2$	**2f**	72[d]
9	**1a**	Ph	Ph	AgOTf	acac	**2g**	77
10	**1a**	Ph	Ph	AgOTf	$CH_2(CO_2Me)_2$	**2h**	80
11	**1a**	Ph	Ph	AgOTf	$CH_2(CN)_2$	**2i**	84
12[e]	**1a**	Ph	Ph	AgOTf	acetone	**2j**	80
13[f]	**1a**	Ph	Ph	$Rh(COD)(PPh_3)_2PF_6$	MeCN	**2k**	61

[a] The reaction was carried out using **1** (1 equiv) and pronucleophiles (2 equiv) in the presence of Lewis acid (3 mol%) in $(CH_2Cl)_2$ at 80 °C within 6 h unless otherwise noted. [b] Isolated yield. [c] The reaction was carried out at 60 °C. [d] Diastereomeric ratio was 84:16. [e] The reaction was carried out in acetone as solvent at 70 °C. [f] The reaction was conducted with $Rh(COD)(PPh_3)_2PF_6$ catalyst (2 mol%) using CH_3CN as solvent. 1-cC_6H_9 = 1-cyclohexenyl; Tf = trifluoromethanesulfonyl.

derivatives **2g-i** were obtained in moderate to high yields (entries 9-11). The reaction of **1a** with 2 equiv of acetone gave **2j** in a low yield. However, when acetone was used as the solvent, the direct addition proceeded smoothly and **2j** was obtained in 80% yield (entry 12). The reaction with CH_3CN proceeded in a low yield, even when the reaction was carried out in CH_3CN; however, when $Rh(COD)(PPh_3)_2PF_6$ was used as catalyst instead of AgOTf, the corresponding product **2k** was obtained in 61% yield (entry 13).

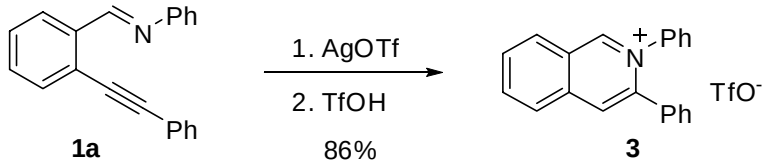
Interestingly, the direct pronucleophile addition could also be applied to the pyridine derivative **1f**; treatment with nitromethane gave the naphthyridine derivative **2l** in 75% yield as shown in Scheme 1.



1f **2l**

Scheme 1

Next, we paid our attention to clarify the reaction mechanism of the present direct Mannich reaction. To know the role of the silver catalyst, we examined the reaction of **1a** with 1 equiv of AgOTf in CH_2Cl_2 in the absence of any pronucleophiles. Interestingly, **1a** was consumed at rt for 2 h and the reaction was quenched by addition of TfOH. After the standard work-up process, a crude material was recrystallized from a mixture of hexane and EtOH to give isoqunolinium salt **3** in 86% yield (Scheme 2).



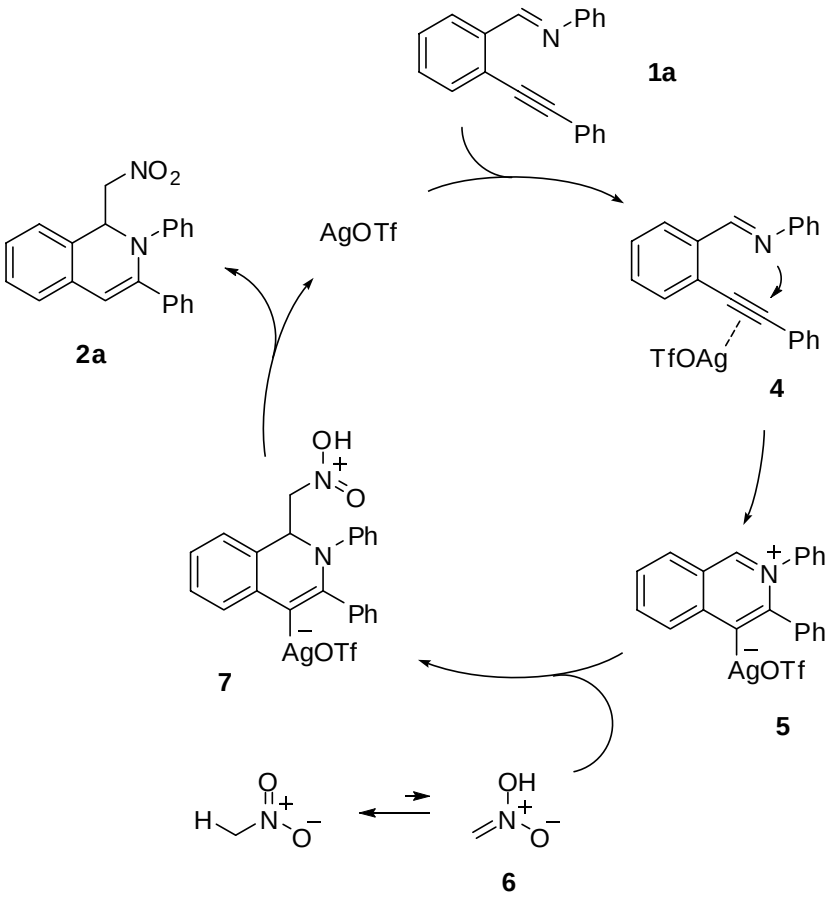
1a **3**

Scheme 2

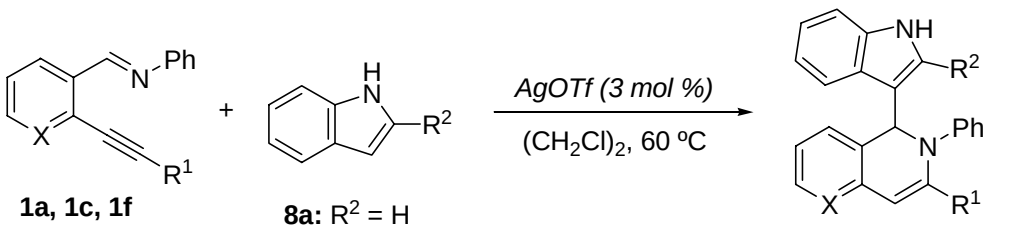
This result clearly indicates that, at the beginning of the cyclization, the triple bond coordinates to the Lewis acid as shown in **4** (Scheme 3). Subsequent attack of the nitrogen atom at the electron deficient triple bond leads to the isoquinolinium intermediate **5**. The addition of aci-nitro-methane **6**, which is derived from nitromethane, gives the product **2** via **7**. As shown in Table 1, the AuCl-catalyzed reaction gave **2a** in a very low yield. Indeed, when **1a** was treated with 1 equiv of AuCl under similar reaction conditions as shown in Scheme 2, the isoqunolinium salt **3** was obtained in 10% yield, which indicats that the formation of the isoquinolinium intermediate **5** is a key step in the present reaction.

Because the 1,2-dihydroisoquinoline derivatives **2** were produced unexpectedly easily from **1**, we were interested in whether other sp^2 and sp carbon pronucleophiles could be used in the present system. To our delight, reactions of **1a,c,f** with indoles **8a-b** and pyrroles **10a-b** proceeded smoothly under the similar

reaction conditions as those given in Table 1 and the corresponding products **9** and **11** were obtained in good to high yields (Schemes 4-5).[8,9] Both indole **8** and pyrrole **10** attacked **1** at their C3-positions exclusively.

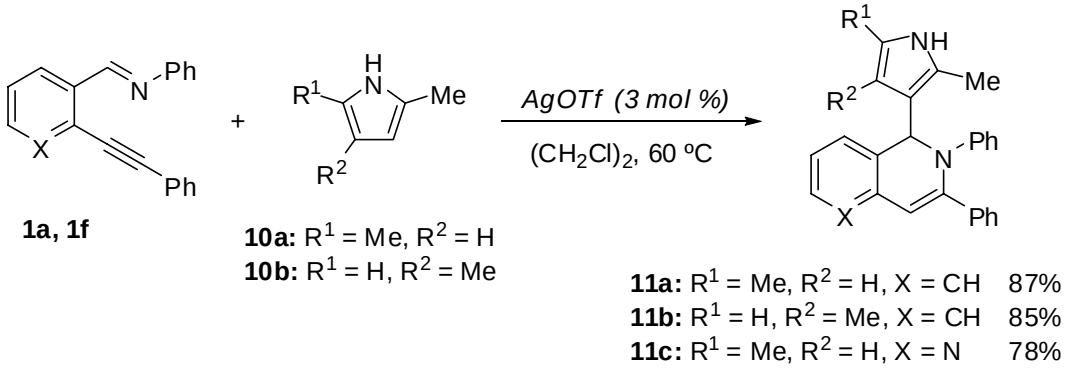


Scheme 3



9a: R^1 = Ph, R^2 = H, X = CH 69%
9b: R^1 = 1-cC_6H_9, R^2 = H, X = CH 66%
9c: R^1 = Ph, R^2 = H, X = N 62%
9d: R^1 = Ph, R^2 = Me, X = CH 74%

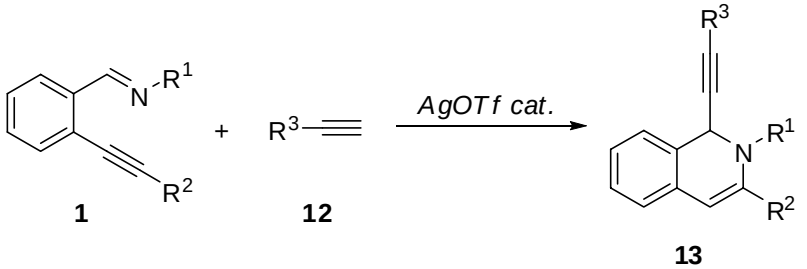
Scheme 4



Scheme 5

Next, we conducted the reactions with terminal alkynes **12** and the results are summarized in Table 2. The reaction of **1a** with phenylacetylene **12a** gave 1-phenylethynyl-1,2-dihydroisoquinoline derivative **13a** in 93% yield. Analogously, the reaction proceeded smoothly with aliphatic alkynes, such as hexyne **12b**, and even with ethyl propiolate **12c**, and the corresponding products **13b** and **13c** were obtained in high yields, respectively (entries 2-3). Not only **1a** but also the other substrates **1b, c** and **f**, which have alkyl groups on the nitrogen atom of the imine moiety, were suitable for the present reaction (entries 4-6). The reaction of **1d**, having a butyl group on the terminus of the alkynyl group, with **12a** also gave **13g** in 58% yield (entry 7). Interestingly, the reaction of **1g** with phenylacetylene **12a** gave the 3,4,5,6-tetrahydro-benzo[f]isoquinoline derivative **13h** in 62% yield (Scheme 6). Several methods for direct addition of terminal alkynes to imine compounds have been reported.[10-11] However, it is worth mentioning that the direct addition of alkynes to benzylidene-phenyl-amine, bearing no alkynyl group at the proximal position, did not proceed at all under the present reaction conditions. This result again

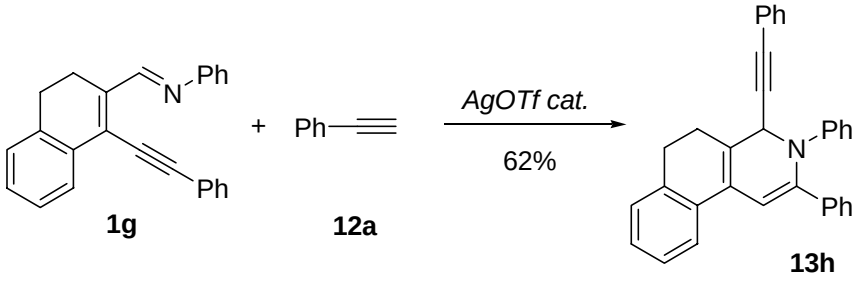
Table 2. Direct addition of terminal alkynes **12** to **1**.[a]



entry	**1**	R^1	R^2	**12**	R^3	**13**	yield (%)[b]
1	**1a**	Ph	Ph	**12a**	Ph	**13a**	93
2	**1a**	Ph	Ph	**12b**	Bu	**13b**	90
3	**1a**	Ph	Ph	**12c**	CO_2Et	**13c**	86
4	**1b**	Bu	Ph	**12a**	Ph	**13d**	42
5	**1c**	Bn	Ph	**12a**	Ph	**13e**	70
6	**1f**	Allyl	Ph	**12a**	Ph	**13f**	70
7	**1d**	Ph	C_4H_9	**12a**	Ph	**13g**	58

[a] The reaction was carried out using **1** (1 equiv) and terminal alkynes **12** (1.2 equiv) in the presence of AgOTf (3 mol%) in $(CH_2Cl)_2$ at 80 °C within 6 h. [b] Isolated yield.

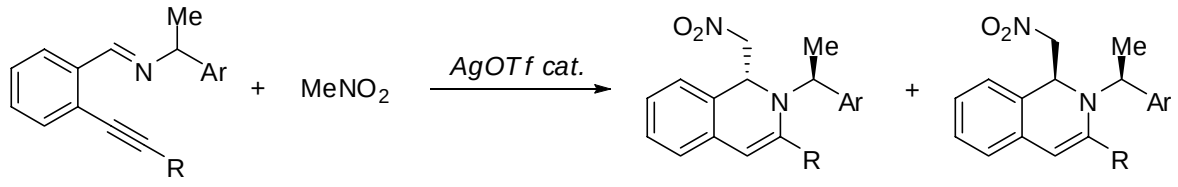
indicates that the presence of *ortho*-alkynyl group is essential for the imine addition and the formation of the isoquinolinium intermediate **5** is a key step.



Scheme 6

We next turned our attention to the stereoselective synthesis of 1,2-dihydroisoquinolines by use of imine **14**, which was derived from *ortho*-alkynylbenzaldehyde with 1-arylethylamine, and the results are summarized in Table 3. Treatment of imine **14a**, derived from 1-phenylethylamine, with nitromethane in the presence of a catalytic amount of AgOTf afforded a mixture of diastereomers **15a** in 41% yield and anti-isomer was obtained selectively over syn-**15a** with 89:11 ratio (entry 1). The use of 1-(1-naphthyl)ethylamine improved the selectivity and anti-**15b** was obtained with 94:6 ratio (entry 2). The reaction with $AgSbF_6$ catalyst decreased the selectivity (entry 3). Optimization experiments revealed that THF was a suitable solvent for the current transformation and the selectivity was increased up to >95:5 (entry 5). High diastereoselectivities were obtained even with other imines **14c-d**, having butyl and cyclohexenyl group at the terminus of the alkynyl group, together with good chemical yields (entries 6-7). The structure of anti-**15c** was unambiguously confirmed by X-ray analysis (Figure 1).

Table 3. Diastereoselective addition of nitromethane to **14**.[a]



Entry	**14**	Ar	R	Solvent	**15**	Yield (%)[b]	anti:syn
1	**14a**	Ph	Ph	$(CH_2Cl)_2$	**15a**	41	89:11
2	**14b**	1-naphthyl	Ph	$(CH_2Cl)_2$	**15b**	56	94:6
3[c]	**14b**	1-naphthyl	Ph	$(CH_2Cl)_2$	**15b**	49	61:39
4	**14b**	1-naphthyl	Ph	toluene	**15b**	50	93:7
5	**14b**	1-naphthyl	Ph	THF	**15b**	57	>95:5
6	**14c**	1-naphthyl	Bu	THF	**15c**	64	92:8
7	**14d**	1-naphthyl	1-cC_6H_9	THF	**15d**	68	>95:5

[a] The reaction was carried out using **14** (1 equiv) and nitromethane (1.2 equiv) in the presence of AgOTf (5 mol%) at rt for 1 d. [b] Isolated yield. [c] $AgSbF_6$ was used as catalyst instead of AgOTf.

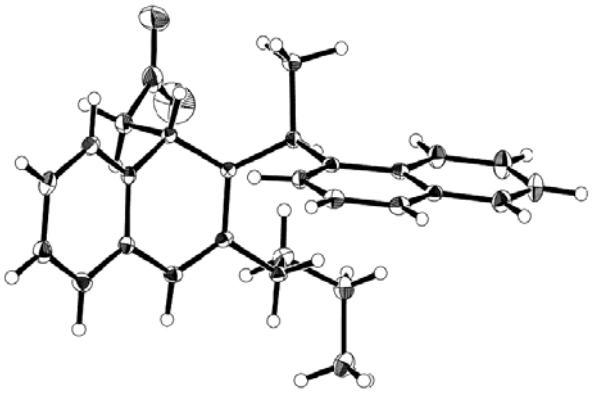


Figure 1. X-Ray structure of anti-**15c**.

Based on the reaction pathway as shown in Scheme 3, the *anti*-stereoselectivity in the reaction of **14** can be accounted for by an allylic strain model, which involves attack of nitromethane on the less hindered bottom face (Figure 2).

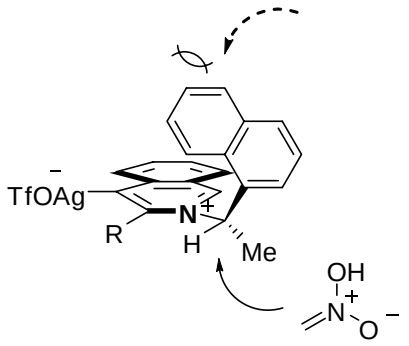


Figure 2

CONCLUSION

We are now in a position to synthesize functionalized 1,2-dihydroisoquinoline skeletons through the direct addition of various carbon pronucleophiles to *ortho*-alkynyl-arylaldimines. Without using the ordinary activated imines bearing an electron-withdrawing group, the addition to imines proceeded well probably due to the in situ formation of the reactive isoquinolinium intermediates **5**. In general, the preparation of a 1-alkyl-1,2-dihydroisoquinolines can be achieved by the nucleophilic addition of a variety of carbon nucleophiles to isoquinolinium salts, which are derived from the corresponding isoquinolines using acylating or alkylating agents.[12] Obviously, the present reaction proceeded without such activation and the current transformation provides an alternative method for the construction of 1,2-dihydroisoquinolines. The protocol can be applied to the diastereoselective synthesis of 1,2-dihydroisoquinolines and high anti-selectivities were observed by use of 1-naphthylethylamine. The observed anti-selectivity was accounted for by an allylic strain model. Further studies to elucidate the precise mechanism of this reaction and to extend the scope of synthetic utility are in progress in our laboratory.

EXPERIMENTAL

General. ^{1}H NMR and ^{13}C NMR spectra were measured on a JEOL JNM-AL 400 (400 MHz) spectrometer. Chemical shift of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane with reference to internal residual $CHCl_3$ (δ = 7.26) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard (δ = 77.0) in $CDCl_3$. IR spectra were measured on a Shimadzu FTIR-8200A Spectrometer. High resolution mass spectra (HRMS) were recorded on BRUKER DALTONICS APEX III spectrometer. Analytical thin layer chromatography (TLC) was performed on a glass plates (Merck Kieselgel 60 F_{254}, layer thickness 0.2 mm). Visualization was accompanied by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid. Column chromatography was performed on silica gel (Merck Kieselgel 70-230 mesh) and basic Chromatorex-NH 200-350 mesh (Fuji Silysia LTD.). All manipulations were carried out under argon atmosphere using standard Schlenk techniques.

General Procedure for the Synthesis of 1,2-dihydroisoquinolines 2. The preparation of **2a** is representative. To a mixture of **1a** (140.7 mg, 0.5 mmol) and AgOTf (3,9mg, 3 mol%) in dichloroethane (1 mL) was added nitromethane (54 μL, 1 mmol) at rt under Ar atmosphere. The resulting mixture was stirred for 1.5 h at 80 °C, then it was cooled to rt. After addition of a saturated aqueous $NaHCO_3$, the mixture was extracted with AcOEt three times. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by basic silica gel column chromatography using a mixture of hexane-AcOEt (8:1 to 5:1) as an eluent to give **2a** in 85% yield (145.5 mg, 0.43 mmol).

Procedure for the Synthesis of 2,3-diphenylisoquinolinium trifluoromethanesulfonate 3. To a solution of **1a** (562 mg, 2 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of AgOTf (514 mg, 2 mmol) in CH_2Cl_2 (5 mL) at rt under Ar atmosphere. The resulting mixture was stirred at rt for 2 h, then trifluoromethanesulfonic acid (1.77 ml, 20 mmol) was added slowly. After the mixture was stirred for 30 min, the solvent was evaporated under reduced pressure. The crude material was recrystallized using EtOH-hexane to give isoquinolinium salt **3** in 86% yield (741.3 mg, 1.72 mmol).

1-(1*H*-Indo-3-yl)-2,3-diphenyl-1,2-dihydroisoquinoline (9a)

Yellow solid; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.19 (m, 1H), 7.68 (br, 1H), 7.56 (m, 2H), 7.56 – 7.14 (m, 14H), 6.92 – 6.88 (m, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.71 (s, 1H), 6.51 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 147.1, 141.2, 137.7, 136.6, 132.3, 131.8, 128.5, 127.6, 127.4, 127.2, 126.3, 125.8, 124.42, 124.41, 123.1, 121.9, 121.7, 121.4, 119.6, 119.2, 118.3, 112.4, 111.3, 61.2; IR (KBr) 3454, 3060, 3035, 1593, 192,

1263, 763, 742 cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{22}N_2$ ($[M + Na]^+$): 421.1681. Found: 421.1675; mp 94 – 98 °C.

3-Cyclohexy-1-enyl-1-(1*H*-indo-3-yl)-2-phenyl-1,2-dihydroisoquinoline (9b)

White powder; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.08 (s, 1H), 7.67 (s, br, 1H), 7.26 – 7.19 (m, 11H), 6.97 (m, 1H), 6.57 (s, 1H), 6.45 (s, 1H), 6.36 (s, 1H), 6.14 (s, 1H), 2.21 – 2.11 (m, 2H), 1.96 (m, 2H), 1.54 – 1.46 (m, 4H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.3, 143.3, 136.5, 133.4, 132.2, 131.9, 129.3, 128.5, 127.1, 125.9, 125.8, 124.3, 123.4, 121.7, 121.1, 120.9, 119.5, 119.4, 118.2, 111.2, 110.3, 76.3, 61.3, 26.4, 25.8, 22.9, 22.0; IR (KBr) 3433, 3055, 2929, 2593, 2488, 2454, 1095, 767, 734 cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{26}N_2$ ($[M + Na]^+$): 425.1988. Found: 425.1989; mp 194 – 197 °C.

5-(1*H*-Indol-3-yl)-6-diphenyl-5,6-dihydro[1,6]naphthyridine (9c)

Yellow solid; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.32 (br, s, 1H), 8.48 (d, J = 4.64 Hz, 1H), 8.15 (d, J = 7.80 Hz, 1H), 7.58 (dd, J = 6.12, 2.44 Hz, 2H), 7.52 (d, J = 7.32 Hz, 1H), 7.40 (d, J = 7.56 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.21 – 7.15 (m, 8H), 7.06 – 7.02 (m, 2H), 6.98 – 6.94 (m, 1H), 6.88 (s, 1H), 6.55 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 150.7, 147.9, 146.8, 146.3, 136.9, 136.4, 133.0, 128.5, 128.3, 128.2, 127.8, 127.0, 124.9, 122.9, 122.6, 122.4, 121.9, 120.8, 119.6, 118.7, 117.5, 111.6, 111.2, 61.6; IR (KBr) 3412, 3057, 3012, 1575, 1492, 1436, 1269, 742, 696 cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{22}N_2$ ($[M + H]^+$): 400.1813. Found: 400.1809; mp 108 – 111 ^{o}C.

1-(2-Methyl-1*H*-indol-3-yl)-2,3-diphenyl-1,2-dihydroisoquinoline (9d)

Yellow solid; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, J = 8.06 Hz, 1H), 7.80 (br, s, 1H), 7.44 – 7.41 (m, 2H), 7.26 (m, 1H), 7.24 (m, 1H), 7.18 – 7.11 (m, 5H), 7.09 – 6.99 (m, 7H), 6.83 (t, J = 12.11 Hz, 1H), 6.53 (s, 1H), 6.49 (s, 1H), 2.40 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.7, 142.7, 138.4, 135.1, 132.2, 131.7, 130.9, 128.2, 128.0, 127.5, 127.4, 127.0, 126.9, 126.2, 126.1, 124.1, 122.9, 121.9, 121.1, 119.9, 119.7, 118.1, 110.1, 109.9, 61.4, 12.8; IR (KBr) 3402, 3057, 2922, 1595, 1490, 1452, 761, 752, 698 cm^{-1}; HRMS (ESI) Calcd. for $C_{30}H_{24}N_2$ ($[M + Na]^+$): 435.1832. Found: 435.1836; mp 109 – 112 ^{o}C.

1-(2,5-Dimethyl-1*H*-pyrrol-2-yl)-2,3-phenyl-1,2-dihydroisoquinoline (11a)

Yellow solid; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.59 (m, 2H), 7.37 (br, s, 1H), 7.33 – 7.24 (m, 5H), 7.20 – 7.11 (m, 4H), 7.04 (m, 2H), 6.87 (t, J = 7.32 Hz, 1H), 6.60 (s, 1H), 6.05 (s, 1H), 5.94 (d, J = 2.44 Hz, 1H), 2.38 (s, 3H), 2.14 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 147.7, 141.6, 138.2, 133.6, 131.5, 128.2, 128.0, 127.5, 127.4, 126.7, 126.2, 125.5, 125.2, 124.1, 122.9, 121.8, 121.1, 119.8, 111.2, 105.4, 61.5, 13.0, 11.8; IR (KBr) 3448, 2952, 2920, 1595, 1560, 1492, 1265, 761, 696 cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{24}N_2$

([M + Na]$^+$): 399.1837. Found: 399.1833; mp 105 – 108 ^{o}C.

1-(3,5-Dimethyl-1*H*-pyrrol-2-yl)-2,3-phenyl-1,2-dihydroisoquinoline (11b)

Yellow solid; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.95 (br, s, 1H), 7.61 – 7.58 (m, 2H), 7.40 – 7.16 (m, 9H), 7.12 – 7.08 (m, 2H), 6.94 (m, 1H), 6.62 (s, 1H), 6.22 (s, 1H), 5.79 (s, 1H), 2.51 (s, 3H), 2.14 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 147.2, 142.6, 137.6, 131.8, 130.9, 129.8, 128.4, 128.3, 127.9, 127.6, 127.2, 126.8, 126.4, 125.8, 124.2, 122.4, 122.0, 112.6, 109.9, 107.6, 59.9, 13.1, 11.6; IR (KBr) 3448, 2952, 2920, 1595, 1560, 1492, 1265, 761, 696 cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{24}N_2$ ([M + Na]$^+$): 399.1837. Found: 399.1832; mp 80 – 84 ^{o}C.

5-(2,5-Dimethyl-1*H*-pyrrol-3-yl)-6.7-diphenyl-5.6-dihydro-1[1,6]naphthyridine (11c)

Yellow solid; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.44 (dd, *J* = 4.88, 1.48 Hz, 1H), 8.38 (s, 1H), 7.60 (m, 2H), 7.34 (d, *J* = 7.56, 1H), 7.26 (m, 3H), 7.14 (m, 2H), 7.04 (m, 3H), 6.93 (t, *J* = 7.32 Hz, 1H), 6.74 (s, 1H), 6.04 (m, 2H), 2.43 (s, 3H), 2.16 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 150.6, 147.6, 147.2, 146.6, 137.5, 132,7, 128.3, 128.2, 128.0, 127.9, 125.7, 122.6, 122.4, 122.1, 120.7, 119.6, 110.3, 104.9, 100.3, 61.7, 12.9, 11.8; IR (KBr) 3134, 3030, 2995, 1596, 1578, 1398, 1271, 769, 752, 700 cm^{-1}; HRMS (ESI) Calcd. for $C_{26}H_{23}N_2$ ([M + H]$^+$): 378.1965. Found: 378.1963; mp 102 – 106 ^{o}C.

***anti*-1-Nitromethyl-3-phenyl-2-(1-phenyl-ethyl)-1,2-dihydroisoquinoline (anti-15a)**

Yellow powder; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 7.32 Hz, 2H), 7.54 – 7.47 (m, 4H), 7.11 – 6.91 (m, 8H), 6.67 (d, *J* = 7.56 Hz, 1H), 6.31 (s, 1H), 5.28 (dd, *J* = 10.48, 3.88 Hz, 1H), 4.38 (q, *J* = 7.06 Hz, 1H), 4.17 (dd, *J* =11.00, 4.16 Hz, 1H), 1.57 (d, *J* = 7.08 Hz, 3 H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (major)145.0, 141.7, 137.6, 132.6, 128.9, 128.7, 128.1, 127.7, 127.4, 127.1, 126.3, 126.2, 126.1, 124.9, 123.6, 108.9, 57.1, 55.5, 17.7; IR (KBr) 2974, 1548, 1377, 1126, 808, 761, 698 cm^{-1}; HRMS (EI) Calcd for $C_{24}H_{22}N_2O_2$ (M$^+$): 370.1681. Found: 370.1677.

***anti*-2-(1-Naphthalen-1-yl-ethyl)-1-nitromethyl-3-phenyl-1,2-dihydroisoquinoline (anti-15b)**

White crystal; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, *J* = 7.36 Hz, 2H), 7.76 (dd, *J* = 6.00, 3.40 Hz, 1H), 7.63 – 7.51 (m, 6H), 7.37 – 7.26 (m, 3H), 6.89 (t, *J* = 7.32 Hz, 1H), 6.79 (t, *J* = 7.32 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.52 (d, *J* = 7.32 Hz, 1H), 6.15 (s, 1H), 5.43 (dd, *J* = 10.70, 3.90 Hz, 1H), 5.24 (q, *J* = 6.84 Hz, 1H), 4.61 (t, *J* = 10.70 Hz, 1H), 4.16 (dd, *J* = 11.0, 3.90 Hz, 1H), 1.74 (d, *J* = 6.90 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 144.7, 138.9, 137.6, 133.3, 132.3, 131.3, 128.9, 128.6, 128.1, 127.8, 127.5, 127.3, 126.2, 126.0, 124.9, 124.4, 124.2, 124.1, 123.5, 123.2, 122.9, 109.3, 76.6, 55.7, 52.9, 19.7; IR (KBr) 3060, 1595, 1546, 1492, 1263, 1136, 1031, 767, 698 cm^{-1}; HRMS (EI) Calcd for $C_{28}H_{24}N_2O_2$ (M$^+$): 420.1838.

Found: 420.1836; mp 129 – 132 °C.

***anti*-3-Butyl-2-(1-naphthalen-1-yl-ethyl)-1-nitromethyl-1,2-dihydroisoquinoline (anti-15c)**

Colorless crystal; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, *J* = 8.40 Hz, 1H), 7.69 (d, *J* = 8.40 Hz, 1H), 7.62 (d, *J* = 8.00 Hz, 1H), 7.32 – 7.16 (m, 4H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.89 – 6.80 (m, 2H), 6.50 (d, *J* = 7.20 Hz, 1H), 5.80 (s, 1H), 5.58 (q, *J* = 6.80 Hz, 1H), 5.27 (dd, *J* = 9.60, 4.40 Hz, 1H), 4.54 (t, *J* = 10.00 Hz, 1H), 4.06 (dd, *J* = 10.80, 4.40 Hz, 1H), 2.47 – 2.39 (m, 1H), 2.28 – 2.20 (m, 1H), 1.68 (m, 5H), 1.48 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 145.1, 138.7, 133.5, 132.6, 130.8, 128.7, 127.7, 127.6, 125.6, 125.22, 125.21, 124.9, 124.6, 123.4, 122.6, 122.3, 105.0, 76.6, 56.3, 53.2, 32.9, 30.4, 22.7, 20.9, 13.9; IR (KBr) 2966, 2920, 1546, 1417, 1151, 804, 779 cm^{-1}; HRMS (EI) Calcd for $C_{26}H_{28}N_2O_2$ (M^+): 400.2151. Found: 400.2149; mp 122 – 125 °C.

***anti*-3-Cyclohex-1-enyl-2-(1-naphthalen-1-yl-ethyl)-1-nitromethyl-1,2-dihydroisoquinoline (anti-15d)**

Yellow crystal; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.91 (m, 1H), 7.58 (m, 1H), 7.47 (d, *J* = 8.42 Hz, 1H), 7.42 (d, *J* = 8.40 Hz, 1H), 7.31 – 7.24 (m, 3H), 6.88 – 6.77 (m, 2H), 6.63 – 6.57 (m, 2H), 6.36 (m, 1H), 5.88 (s, 1H), 5.40 (q, *J* = 6.80 Hz, 1H), 5.30 (dd, *J* = 10.40, 3.60 Hz, 1H), 4.47 (t, *J* = 10.80 Hz, 1H), 4.09 (dd, *J* = 11.2, 4.00 Hz, 1H), 2.50 (m, 1H), 2.28 – 2.22 (m, 3H), 1.89 – 1.73 (m, 4H), 1.66 (d, *J* = 6.80 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 146.1, 139.1, 134.1, 133.3, 132.4, 131.5, 129.7, 127.8, 127.5, 126.7, 125.8, 124.9, 124.6, 124.5, 124.4, 123.5, 123.0, 107.0, 76.6, 55.6, 52.8, 27.1, 26.0, 23.0, 22.4, 19.7; IR (KBr) 2983, 2929, 1633, 1596, 1396, 1259, 1139, 1047, 1029, 925, 779, 750 cm^{-1}; HRMS (EI) Calcd for $C_{28}H_{28}N_2O_2$ (M^+): 424.2151. Found: 424.2148; mp 143 – 146 °C.

X-Ray Crystallographic Analysis. Single crystals of anti-**15c** suitable for X-ray diffraction study were obtained by recrystallization from hexane/CH_2Cl_2 at rt. X-ray data were collected on a Rigaku Saturn CCD diffractometer with graphite-monochromated Mo Kα radiation (λ 0.71070 Å). The data were corrected for Lorentz and polarization effects. The structures were solved by direct methods and refined by full-matrix least-squares against F^2 using the CrystalStructure crystallographic software package.[13,14]

Crystal Data of anti-**15c.** $C_{26}H_{28}N_2O_2$, M_w = 400.52, colorless prism, 0.20×0.20×0.15 mm, triclinic, space group P-1 (#2), *a* = 10.254(3) Å, *b* = 10.656(4) Å, *c* = 11.184(3) Å, α = 68.826(15)º, *β* = 70.071(15)º, γ = 77.726(17)º, *V* = 1065.6(6) Å^3, *T* = 173 K, Z = 2, μ(Mo Kα) = 0.789 cm^{-1}, 14511 reflections measured, 4794 unique (R_{int} = 0.041). The final *R*1 and *wR*2 were 0.0457 ($I > 2.00\sigma(I)$) and 0.0749 (for all data), respectively. Crystallographic data (excluding structure factors) for the structure of anti-**15c** have been deposited with the Cambridge Crystallographic Data Center as supplementary

publication no. CCDC 679280. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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