Literature Report (2)

# Enantioselective Double Manipulation of Tetrahydroisoquinolines with Terminal Alkynes and Aldehydes under Copper(I) Catalysis

**Reporter: Ji Y.**
**Checker: Guo R. N.**
**Date: 2014/04/08**

Ma, S. *et al*.
*Angew. Chem. Int. Ed.* **2014**, *53*, 277.

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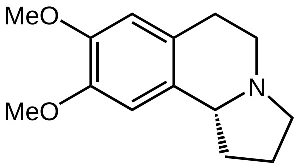
# Introduction

**1986年毕业于杭州大学化学系；**
**1986年至1990年就读于中国科学院上海有机化学研究所，并于1990年12月获得博士学位；**
**1992年9月至1993 年10月瑞士苏黎世联邦理工学院(ETH)博士后；**
**1993年10月至1997年3月美国普渡大学博士后；**
**2005年11月当选为中国科学院院士。**

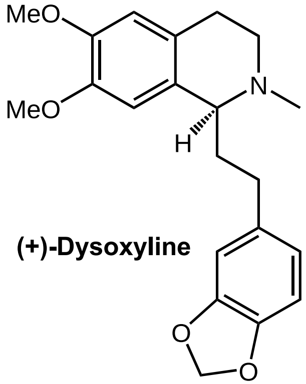
麻生明

研究领域：
金属参与的联烯化学；
联烯亲电加成反应的立体化学及区域选择性调控；
亚烷基环丙烷及环丙烯的选择性碳-碳键断裂；
多中心反应，取得了一些创新性研究成果，发现了立体化学控制开关、碳-碳双键的长距离“移走”、多种联烯间的反应

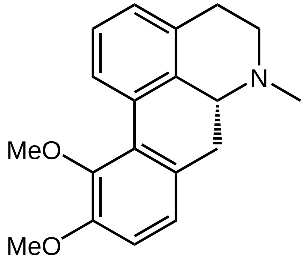
# Introduction



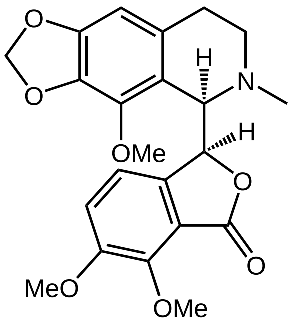

**(+)-Crispine A**



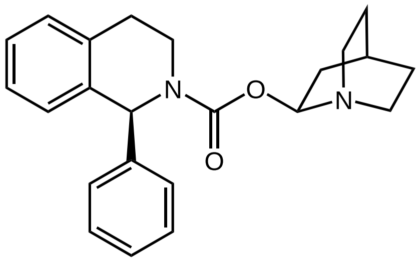

**(+)-Dysoxyline**




**Apomorphine**

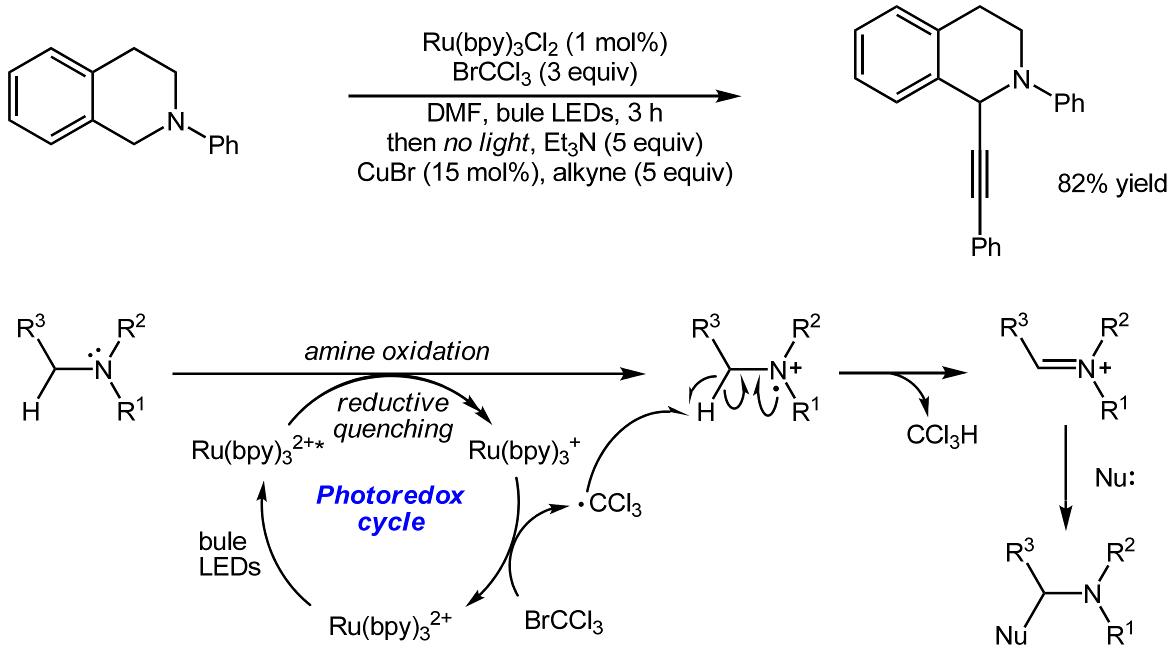



**Nascapine**




**Solifenacin**

# C1-Alkynation of THIQs :
## via Visible-light Photoredoxcatalysis

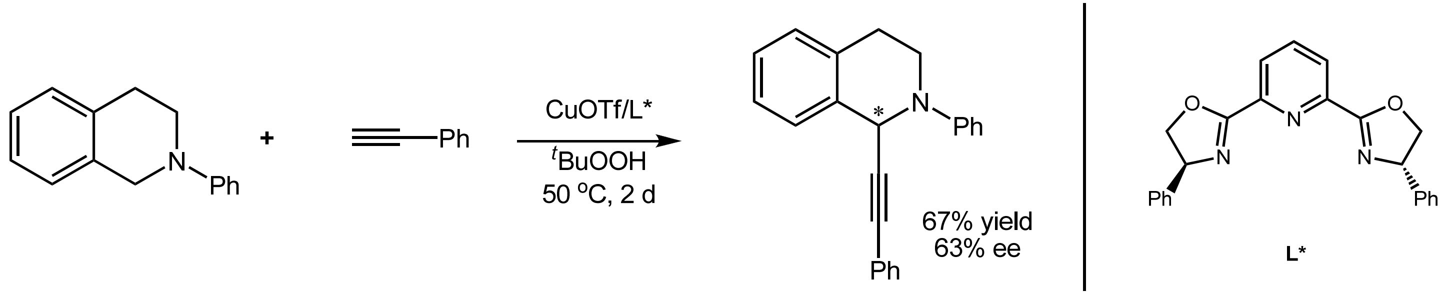



Stephenson C. R. J. *et al. J. Am. Chem. Soc.* **2010**, *132*, 1464

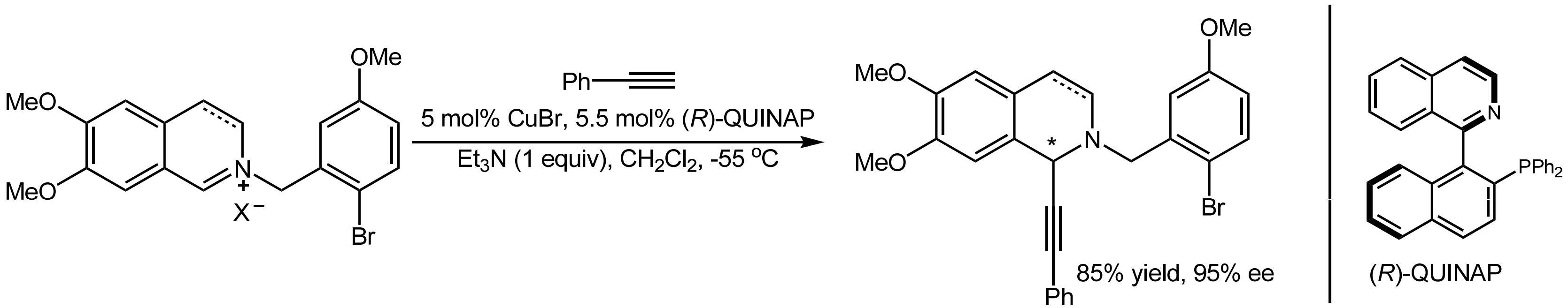
Stephenson C. R. J. *et al. Org. Lett*. **2012**, *14*, 94.

# C1-Alkynation of THIQs :
## via the Cross Dehydrogenative-Coupling (CDC)

### 1. Stoichimetric Exogenous Oxidant

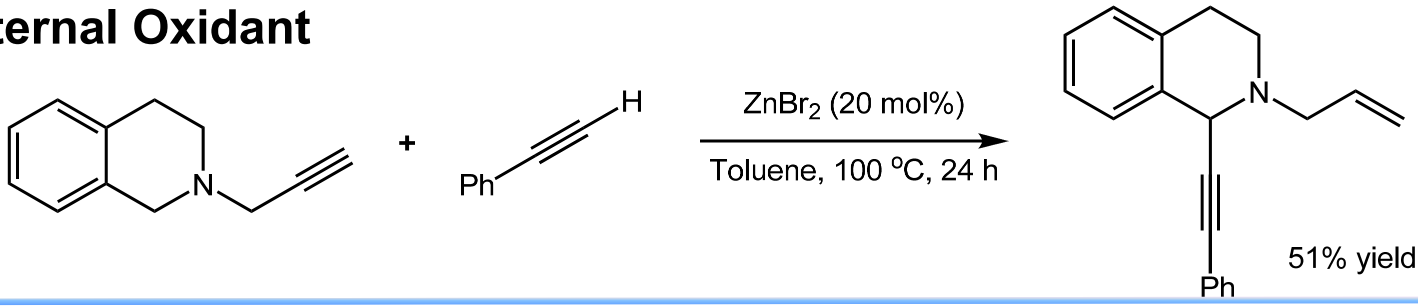


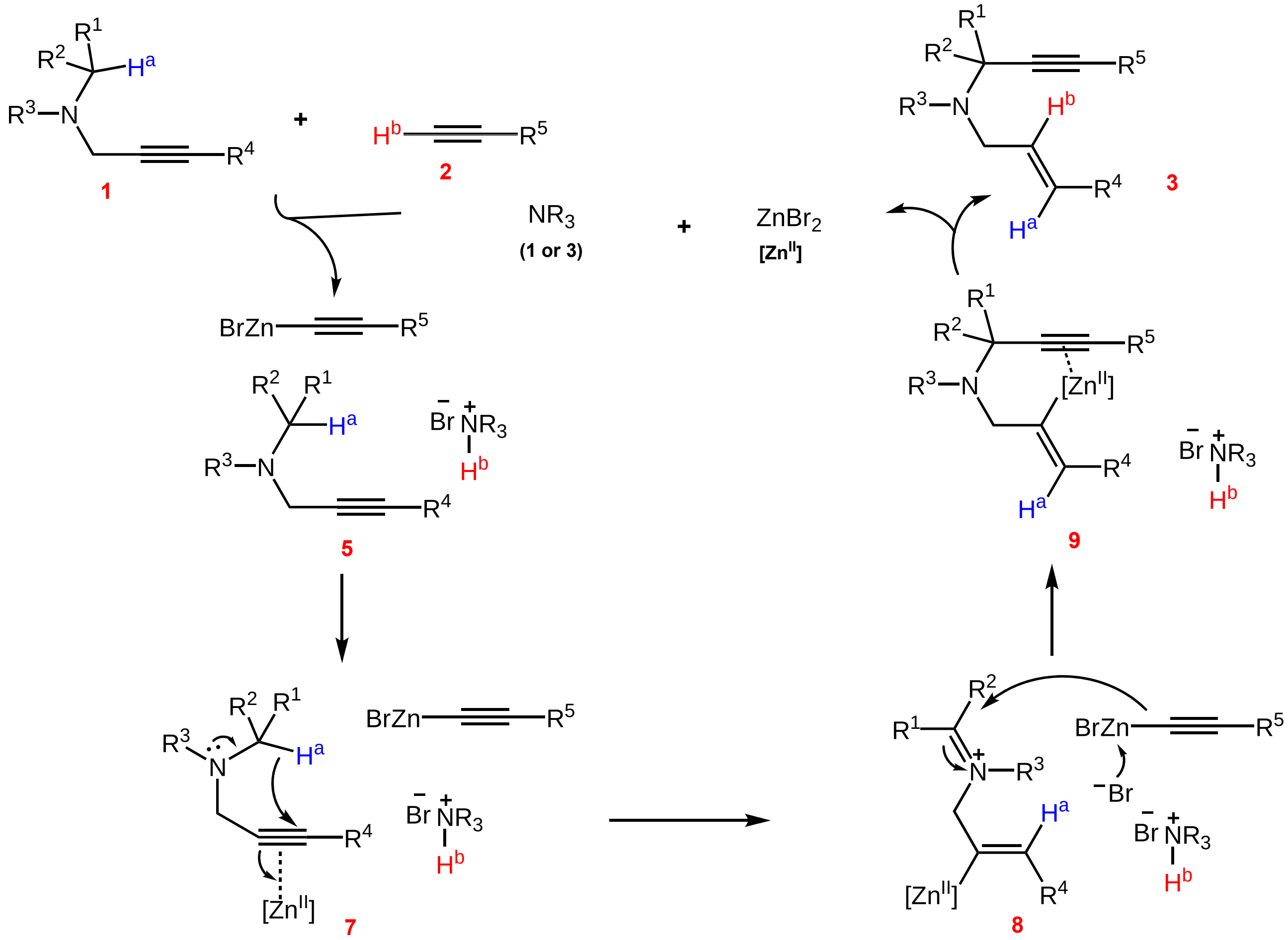

### 2. Isoquinoline Iminium




Li, C. J. *et al. Org. Lett*. **2004**, *6*, 4997.
Schreiber, S. L. *et al. Org. Lett*. **2006**, *8*, 143.

# 3. Internal Oxidant

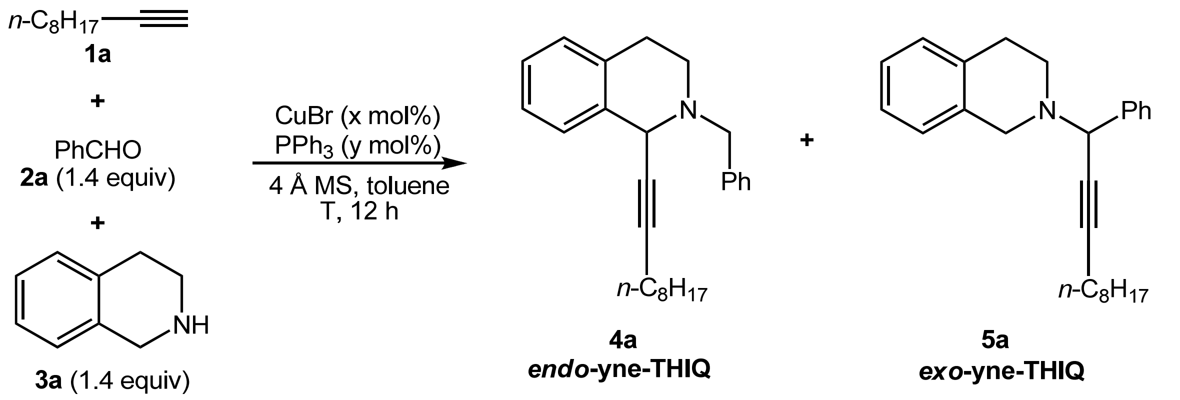



Hiroyuki, N. *et al. J. Am. Chem. Soc.* **2012**, *134*, 2504

# C1-Alkynation of THIQs :
## via A[3] Reaction with Tunable Iminium Ions

### Optimization of the Catalytic Alkynylation of Tetrahydroisoquinolines




| Entry | x | y | T (°C) | Yield (4a) [a] | Yield (5a) [a] |
|---|---|---|---|---|---|
| 1 | 15 | 0 | RT | 1 | 96 |
| 2 | 5 | 0 | RT | 9 | 13 |
| 3 [b] | 5 | 5.5 | RT | 23 | 1 |
| 4 | 5 | 5.5 | 80 | 88 | 1 |
| 5 | 2.5 | 2.75 | 80 | 90 | N.D. |

***a.*** Determined by $^{1}$H NMR; ***b.*** Conducted for 13 h; N.D. = not determined.

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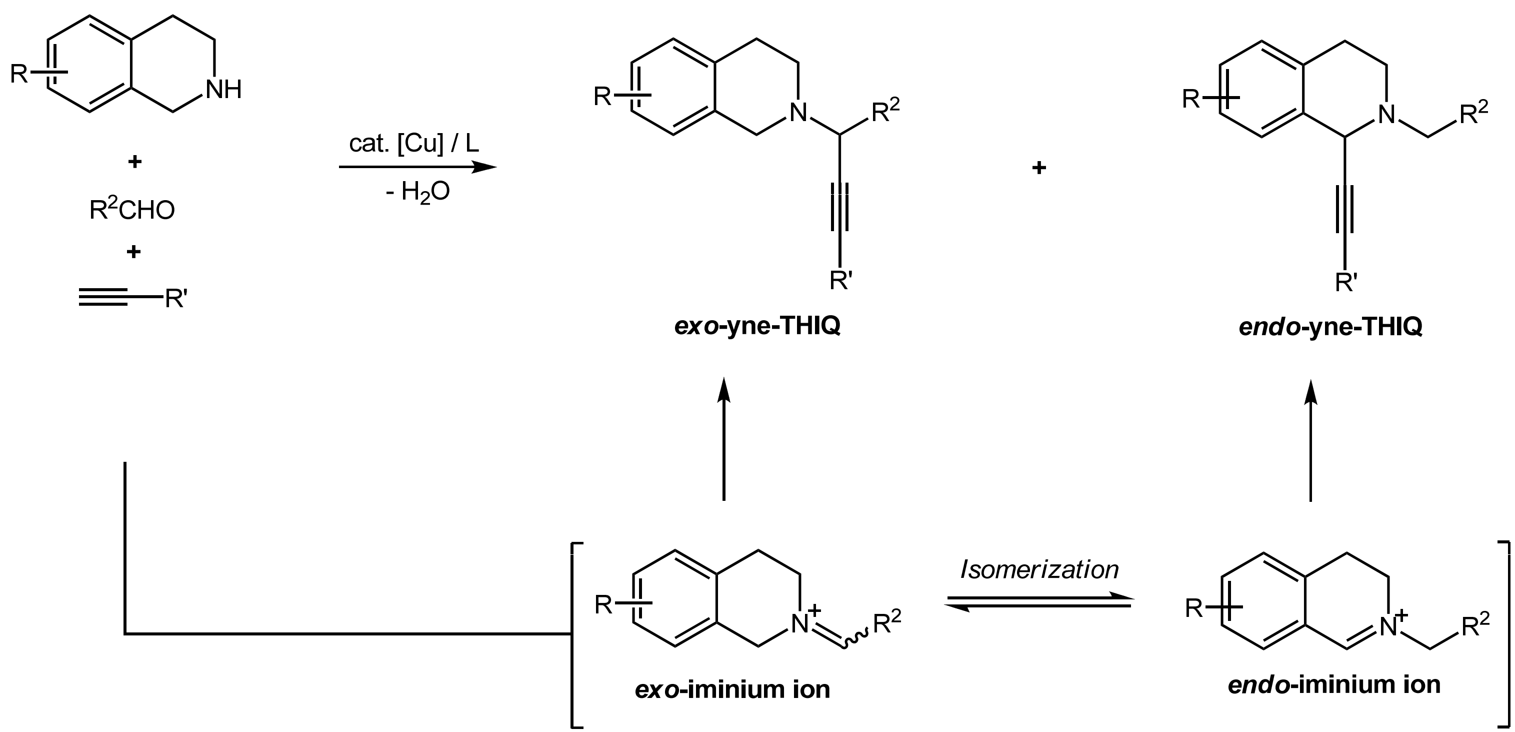
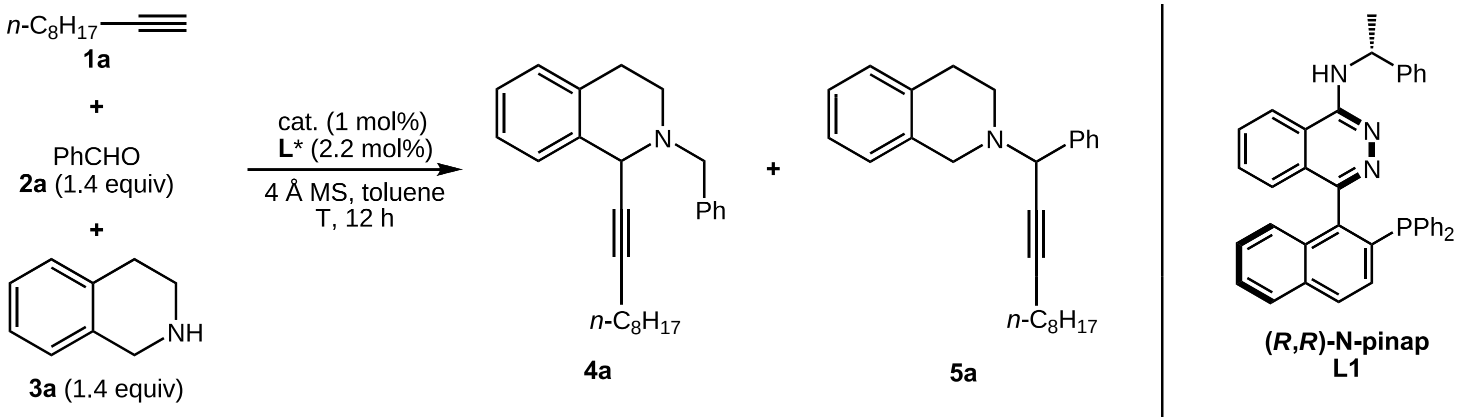
# Approaches to Optically Active Tetrahydroisoquinolines

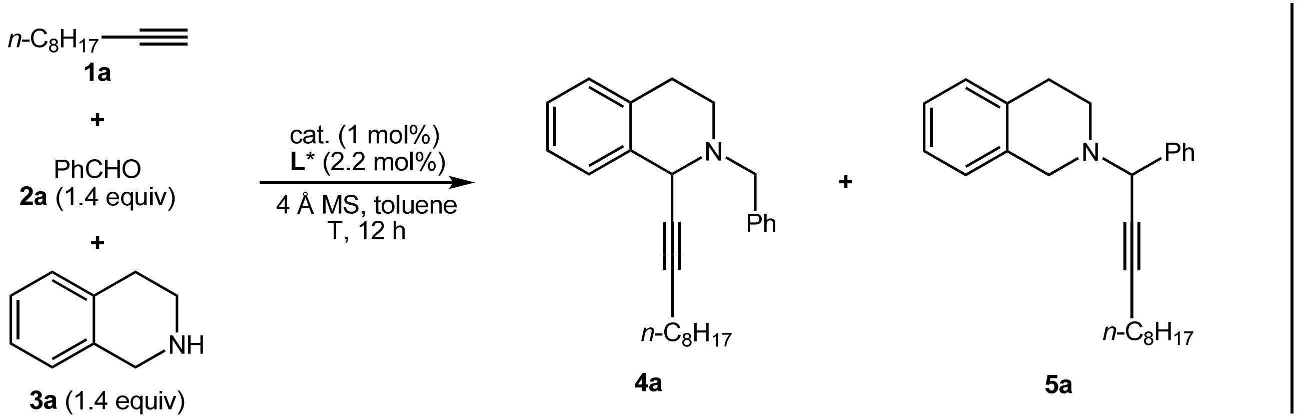


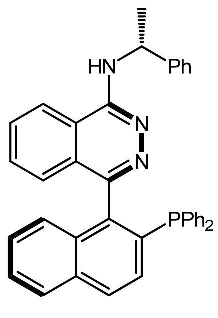
# Optimization of the Catalytic Asymmetric α-Alkynylation of Tetrahydroisoquinolines



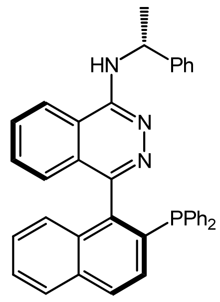

| Entry | Cat . | T (°C) | Ligand | Yield (4a) [a] | Yield (5a) [b] | Ee (%) [c] |
|---|---|---|---|---|---|---|
| 1 [d,e] | CuBr | 80 | **L1** | 97 | 1 | 88 |
| 2 | CuBr | 80 | **L1** | 96 | N.D. | 89 |
| 3 | CuBr | 60 | **L1** | 76 | N.D. | 92 |
| 4 | CuCl | 60 | **L1** | 96 | N.D. | 89 |
| 5 | CuOTf | 60 | **L1** | 98 | N.D. | 88 |
| 6 | CuI | 60 | **L1** | 97 | N.D. | 92 |

***a.*** Isolated yield; ***b.*** Determined by $^{1}H$ NMR; ***c.***Determined by HPLC; ***d.*** CuBr (5 mol%);
***e.*** Ligand (5.5 mol%); ***f.*** PhCOOH (5 mol%) was added.

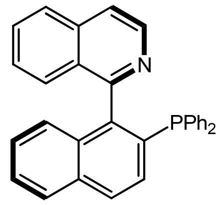


**(*R*,*R*)-N-pinap**
**L1**



**(*R*,*S*)-N-pinap**
**L2**

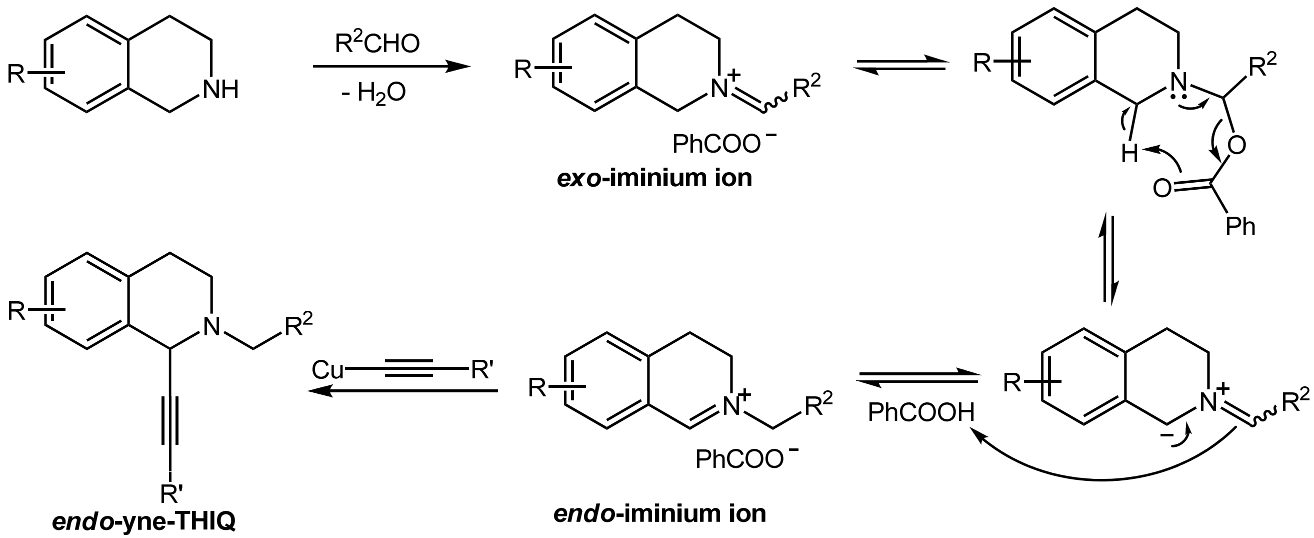


**(*R*)-quinap**
**L3**

| Entry | Cat . | T (°C) | Ligand | Yield (4a) [a] | Yield (5a) [b] | Ee (%) [c] |
|---|---|---|---|---|---|---|
| 8 | CuI | 60 | **L3** | 76 | N.D. | 64 |
| 7 | CuI | 60 | **L2** | 93 | N.D. | - 83 |
| 6 | CuI | 60 | **L1** | 97 | N.D. | 92 |
| 9 | CuI | 40 | **L1** | 84 | N.D. | 94 |
| 10 | CuI | RT | **L1** | 62 | N.D. | 95 |
| 11 [f] | CuI | 40 | **L1** | 98 | N.D. | 94 |

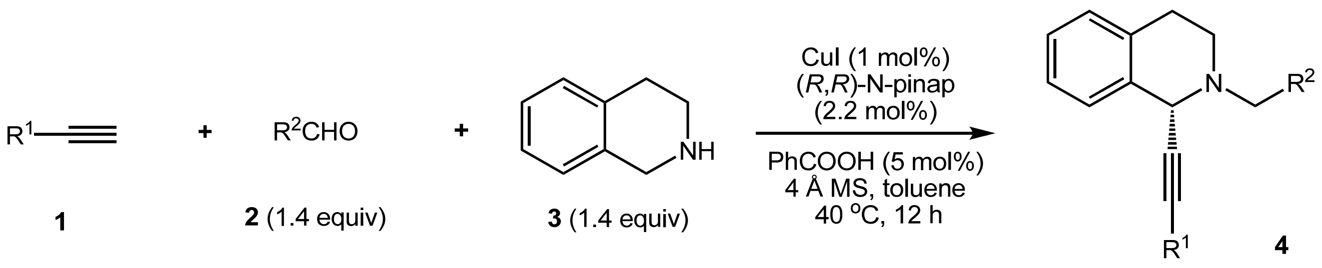
***a.*** Isolated yield; ***b.*** Determined by $^{1}$H NMR; ***c.***Determined by HPLC; ***d.*** CuBr (5 mol%); ***e.*** Ligand (5.5 mol%); ***f.*** PhCOOH (5 mol%) was added.

# Mechanism



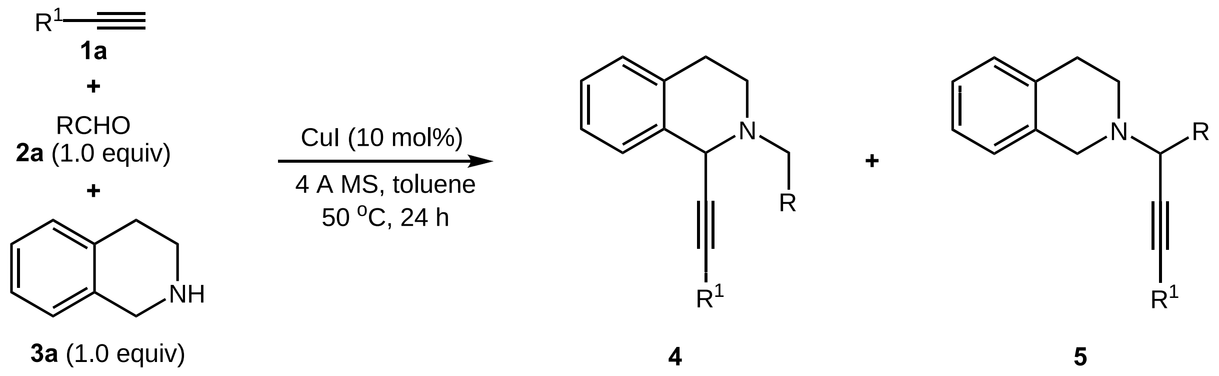
R
NH
$R^2CHO$
- $H_2O$
R
N+
$R^2$
PhCOO⁻
*exo*-iminium ion
R
N
$R^2$
H
O
O
Ph
R
N+
$R^2$
PhCOOH
R
N+
$R^2$
PhCOO⁻
*endo*-iminium ion
Cu
R'
R
N
$R^2$
R'
*endo*-yne-THIQ

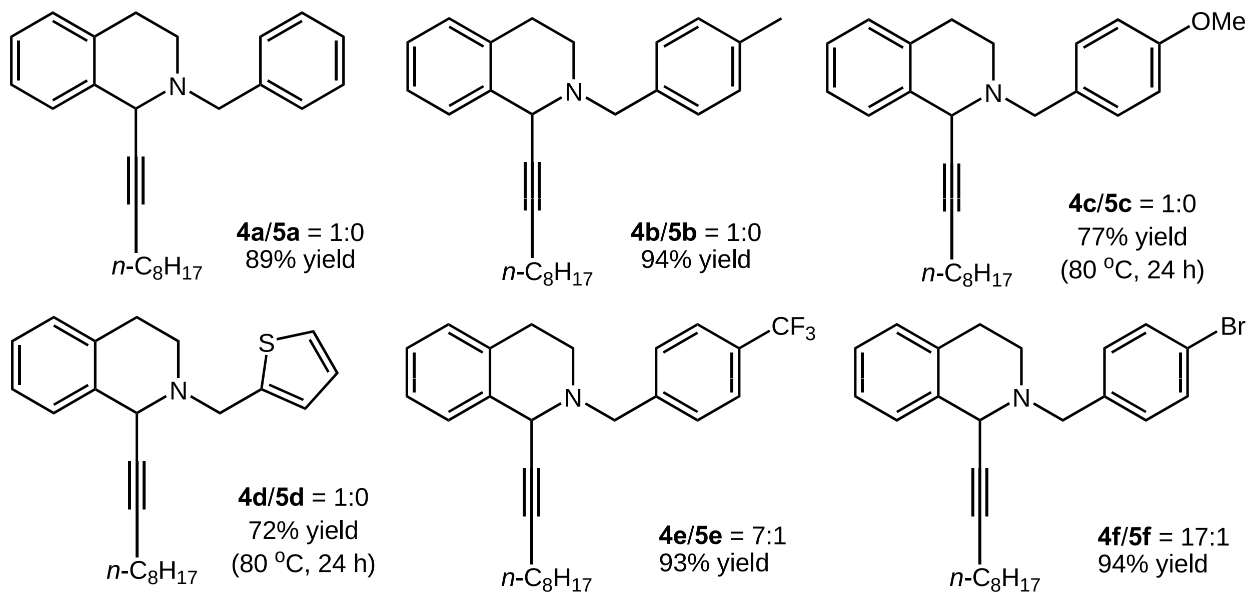
# Scope of the Catalytic Alkynylation of Tetrahydroisoquinolines



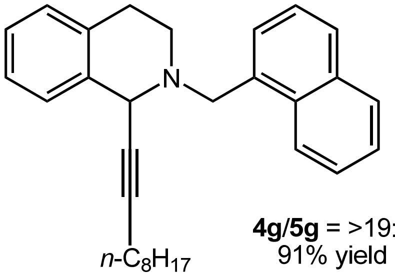

| Entry | $R^1$ | $R^2$ | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | $n$-$C_8H_{17}$ | Ph | 98 | 94 |
| 2 | Cy | Ph | 94 | 95 |
| 3 | $TBSO(CH_2)_2$ | Ph | 96 | 93 |
| 4 | Ph | Ph | 94 | 95 |
| 5 | 4-$FC_6H_4$ | Ph | 95 | 94 |
| 6 | 4-$MeOC_6H_4$ | Ph | 97 | 93 |
| 7 | $n$-$C_8H_{17}$ | 4-$MeC_6H_4$ | 95 | 94 |
| 8 | $n$-$C_8H_{17}$ | 4-$FC_6H_4$ | 97 | 95 |
| 9 | $n$-$C_8H_{17}$ | 2,6-$Cl_2C_6H_3$ | 89 | 93 |
| 10 | $n$-$C_8H_{17}$ | N-Ts-indole-3- | 80 | 92 |

# C1-Alkynation of THIQs :
## Via $A^3$ Reaction with Tunable Iminium Ions

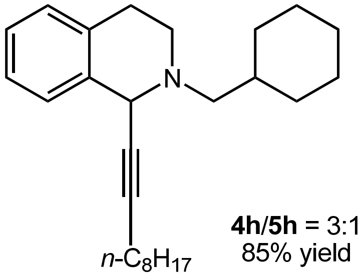


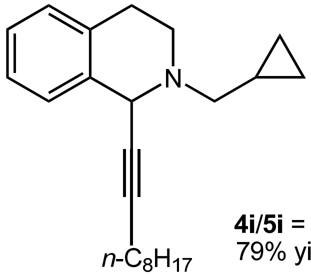

Yu, Z. X. *et al*. *Org. Lett*. **2013**, *15*, 5928.



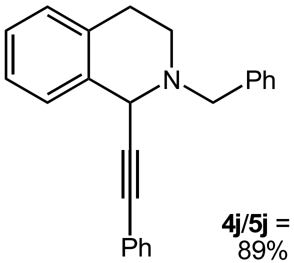

**4g/5g** = >19:1
91% yield



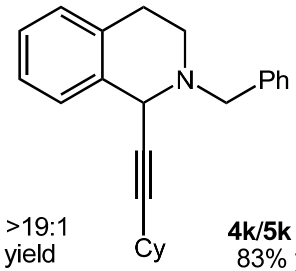

**4h/5h** = 3:1
85% yield



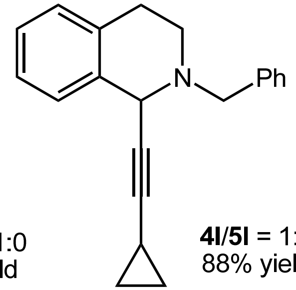

**4i/5i** = 4:1
79% yield



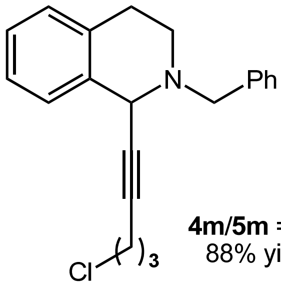

**4j/5j** = >19:1
89% yield



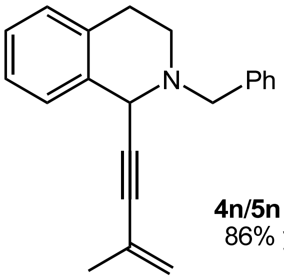

**4k/5k** = 1:0
83% yield



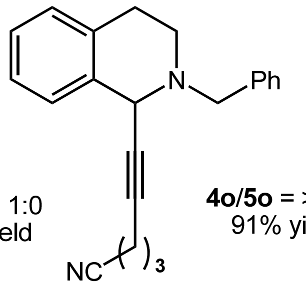

**4l/5l** = 1:0
88% yield



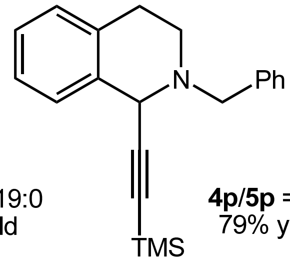

**4m/5m** = 1:0
88% yield



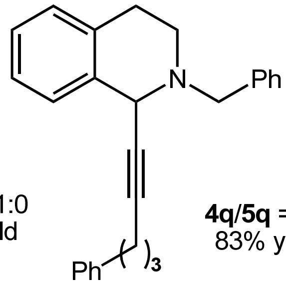

**4n/5n** = 1:0
86% yield



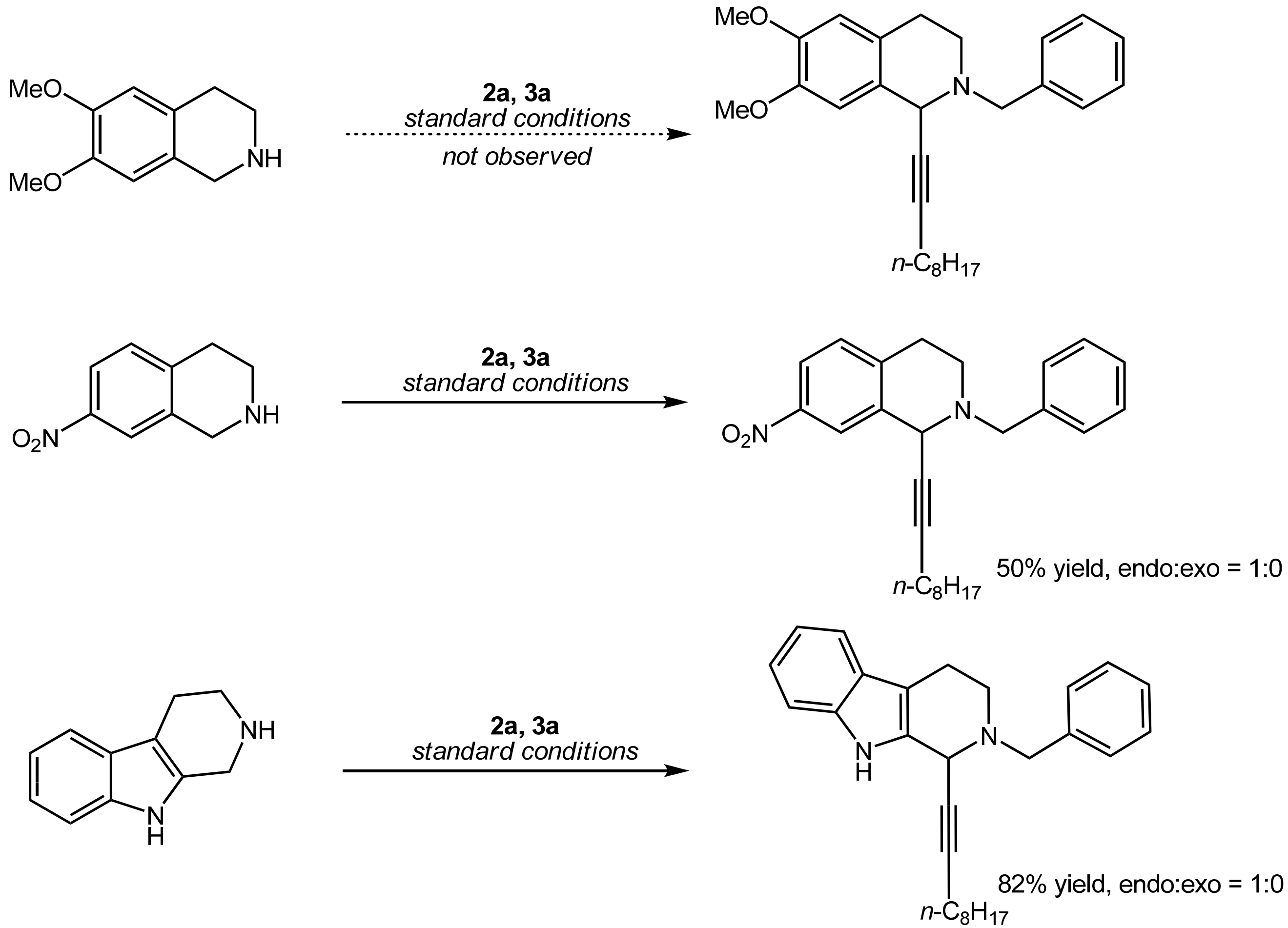

**4o/5o** = >19:0
91% yield




**4p/5p** = 1:0
79% yield




**4q/5q** = 1:0
83% yield

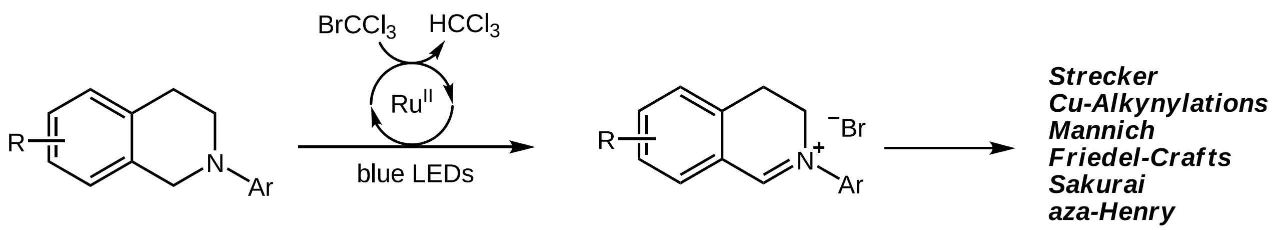



Yu, Z. X. *et al*. *Org. Lett*. **2013**, *15*, 5928.

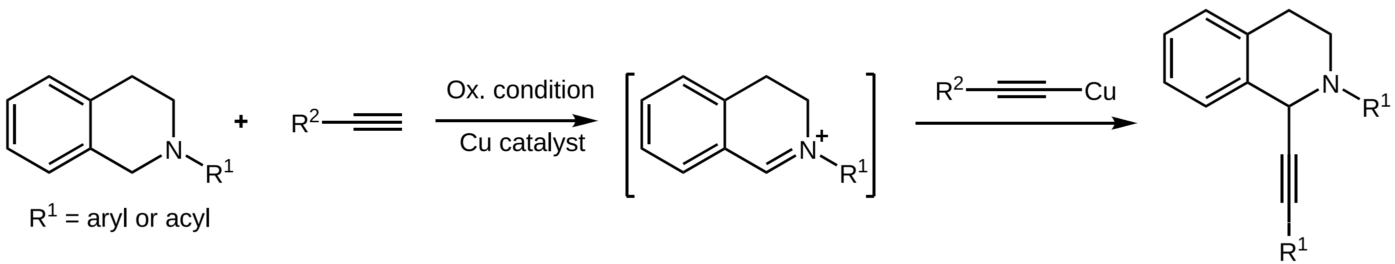
# Summary:

## C1-Alkynylation Strategies of THIQs

### 1) C1-Alkynylation of THIQ Via Visible-light Photoredoxcatalysis



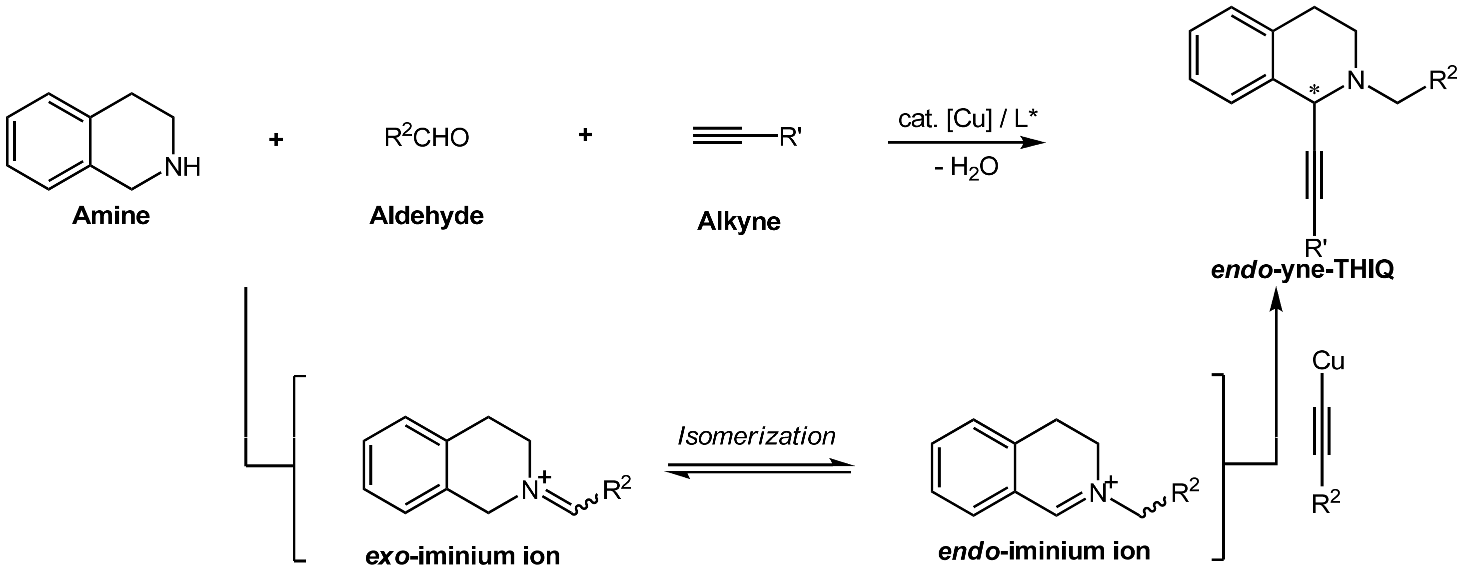

### 2) C1-Alkynylation of THIQ using the Cross Dehydrogenative-Couping (CDC) Strategy



# Summary:

## C1-Alkynylation Strategies of THIQs

### 3) CuI-Catalyzed C1-Alkynylation of THIQ by $A^3$ Reaction with Tunable Iminium Ions



**1,2,3,4-Tetrahydroisoquinolines (THIQs) with a stereogenic center at the C1 position form a large class of natural and unnatural compounds with a great diversity of important biological properties. Representative examples include (+)- crispine A, isolated from *Carduus crispus*, (+)-dysoxyline, isolated from *Dysoxylum lenticellare*, and the drugs apomorphine, nascapine, and solifenacin.**

**In conclusion, we have succeeded in developing a novel CuI-catalyzed highly enantioselective synthesis of chiral tetrahydroisoquinolines through the α-alkynylation of 1,2-unsubstituted tetrahydroisoquinolines with aldehydes and terminal alkynes with readily available N-pinap as the chiral ligand. The low catalyst loading, the mild reaction conditions, the broad scope of the reaction, the efficiency with which the tetrahydroisoquinoline skeleton can be accessed, and the potential for straightforward synthetic manipulation of the *N*-benzyl group and the C-C triple bond make this method of very broad interest to organic and medicinal chemists.**

This research opens a new and efficient entry to a broad range of tetrahydroisoquinolines, since, in principle, different nucleophiles may be applied instead of terminal alkynes. Further studies, including investigations into possible nucleophiles and synthetic applications to natural products (such as (+)-crispine A and (+)-dysoxyline) and drugs, are being actively pursued by our research group.