

# Organometallic Reactions in Aqueous Media

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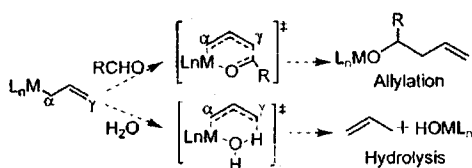


## Theoretical Study of the Intrinsic Reactivities of Various Allylmetals toward Carbonyls and Water<sup>1</sup>

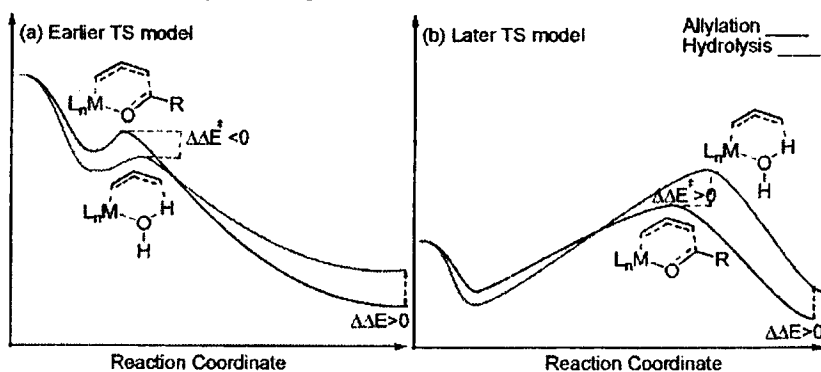
Lung Wa Chung,<sup>\*</sup> Tak Hang Chan,<sup>‡</sup> and Yun-Dong Wu<sup>\*,‡,§</sup> *Organometallics* 2005, 24, 1598-1607

**Table 1.** Natural Charges of  $ML_n$  and  $C_3H_2$ , Calculated Complexation Energies with One Water Molecule, Reaction Energies of Hydrolysis ( $\Delta E_w$ ) and Allylation ( $\Delta E_{C=O}$ ), Thermodynamic Preferences toward Hydrolysis ( $\Delta\Delta E = \Delta E_w - \Delta E_{C=O}$ ), Activation Energies of Hydrolysis ( $\Delta E_w^\ddagger$ ) and Allylation ( $\Delta E_{C=O}^\ddagger$ ), and Kinetic Preferences toward Hydrolysis ( $\Delta\Delta E^\ddagger = \Delta E_w^\ddagger - \Delta E_{C=O}^\ddagger$ ) Obtained by the MP2 Method<sup>a</sup>

|                   | $ML_n$ | $C_3H_2$           | $\Delta E_{C=O}$         | $\Delta E_w^\ddagger$ | $\Delta E_{C=O}^\ddagger$ | $\Delta\Delta E^\ddagger$ | $\Delta E_w^\ddagger$ | $\Delta E_{C=O}^\ddagger$ | $\Delta\Delta E^\ddagger$ |
|-------------------|--------|--------------------|--------------------------|-----------------------|---------------------------|---------------------------|-----------------------|---------------------------|---------------------------|
| Li                | 0.91   | -0.48 <sup>b</sup> | -16.5/-18.6 <sup>c</sup> | -28.0                 | -40.6                     | 12.6                      | 0.9                   | 3.2/3.0 <sup>e</sup>      | -2.3/-2.1 <sup>s</sup>    |
| Na                | 0.94   | -0.50 <sup>b</sup> | -17.5/-13.7 <sup>c</sup> | -24.3                 | -37.2                     | 12.9                      | -1.2 <sup>f</sup>     | 4.1 <sup>s</sup>          | -5.3 <sup>s</sup>         |
| K                 | 0.97   | -0.51 <sup>b</sup> | -16.1/-8.1 <sup>c</sup>  | -26.3                 | -37.0                     | 10.7                      | -1.5 <sup>f</sup>     | 8.7 <sup>s</sup>          | -10.2 <sup>s</sup>        |
| ZnBr              | 0.67   | -0.05              | -15.7                    | -16.2                 | -27.3                     | 11.1                      | 12.9                  | 6.9 <sup>s</sup>          | 6.0                       |
| CdBr              | 0.63   | -0.05              | -11.7                    | -10.0                 | -21.2                     | 11.2                      | 15.2                  | 9.0                       | 6.2                       |
| HgBr              | 0.50   | -0.03              | -6.4                     | 2.9                   | -9.1                      | 12.0                      | 27.6                  | 16.9                      | 10.7                      |
| In(I)             | 0.72   | -0.37 <sup>b</sup> | -6.8/-4.1 <sup>c</sup>   | -36.9                 | -46.4                     | 9.5                       | 0.7                   | 5.8 <sup>s</sup>          | -5.1 <sup>s</sup>         |
| InBr <sub>2</sub> | 0.52   | 0.00               | -21.3                    | -16.7                 | -29.0                     | 12.3                      | 12.7                  | 4.7                       | 8.0                       |



**Scheme 2.** Energetic Diagram for Hydrolysis and Allylation Reactions



— Advantages —

- (1) The ease of reactions in obviating the need for inflammable anhydrous organic solvents and inert atmosphere.
- (2) Protection of reactive hydroxy functional groups is no longer required.
- (3) compounds (e.g. carbohydrates) insoluble in organic solvents can react directly.

ORGANOMETALLIC REACTIONS IN AQUEOUS MEDIA WITH INDIUM<sup>1</sup>

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Tetrahedron Lett. 1991, 32, 7020.

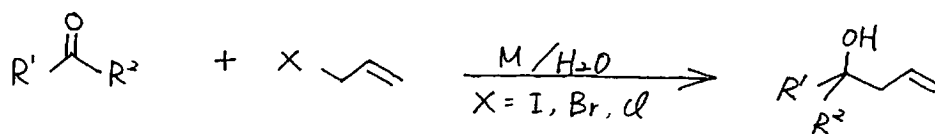


Table 2. Allylation of Aldehydes and Ketones Mediated by Indium in Aqueous Media

| Entry | R <sup>1</sup>   | R <sup>2</sup>  | X  | Metal | Δ/AlkylX/M | Time(hrs) | Yield            | Strain <sup>1</sup> |
|-------|--|-----------------|----|-------|------------|-----------|------------------|---------------------|
| 1     | Ph   | H               | Br | In    | 1/1.5/1    | 3         | 97               |                     |
| 2     | Ph   | H               | I  | In    | 1/1.5/1    | 3         | 95               |                     |
| 3     | Ph   | H               | Cl | In    | 1/1.5/1    | 5         | 60               |                     |
| 4     | Ph   | H               | Cl | Sn    | 1/1.5/1    | 5         | 0 <sup>a,b</sup> |                     |
| 5     | ClPh   | H               | Br | In    | 1/1.5/1    | 1         | 94               |                     |
| 6     | CH <sub>2</sub> CHOH   | H               | Br | In    | 1/1.5/1    | 3         | 85               | 67:33               |
| 7     | CH <sub>2</sub> CH(ODCB)   | H               | Br | In    | 1/1.5/1    | 3         | 75               | 24:76               |
| 8     | CH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> CH(OR <sup>a</sup> ) | H               | Br | In    | 1/1.5/1    | 3         | 80               | 24:76               |
| 9     | PhCH(CH <sub>3</sub> )   | H               | Br | In    | 1/1.5/1    | 3         | 90               | 78:22               |
| 10    | Ph   | CH <sub>3</sub> | Br | In    | 1/1.5/1    | 5         | 72               |                     |
| 11    | Ph   | CH <sub>3</sub> | Br | Zn    | 1/1.5/1    | 5         | 18 <sup>c</sup>  |                     |
| 12    | Ph   | CH <sub>3</sub> | Br | Sn    | 1/1.5/1    | 3         | 0 <sup>d</sup>   |                     |
| 13    | -(CH <sub>2</sub> ) <sub>5</sub> -                                   |                 | Br | In    | 1/1.5/1    | 6         | 68               |                     |
| 14    | -(CH <sub>2</sub> ) <sub>5</sub> -                                   |                 | Br | Sn    | 1/1.5/1    | 6         | 0 <sup>d</sup>   |                     |
| 15    | HOCH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub>                   | H               | Br | In    | 1/1.5/1    | 3         | 85               |                     |
| 16    | HO(CH <sub>2</sub> ) <sub>4</sub>                                    | H               | Br | In    | 1/1.5/1    | 3         | 95               |                     |
| 17    | (CH <sub>2</sub> O) <sub>2</sub> CHCH <sub>2</sub>                   | CH <sub>3</sub> | Br | In    | 1/2/1.5    | 6         | 70               |                     |
| 18    | (CH <sub>2</sub> O) <sub>2</sub> CHCH <sub>2</sub>                   | CH <sub>3</sub> | Br | Zn    | 1/2/2      | 6         | 0                |                     |
| 19    | (CH <sub>2</sub> O) <sub>2</sub> CHCH <sub>2</sub>                   | CH <sub>3</sub> | Br | Sn    | 1/2/2      | 6         | 10 <sup>d</sup>  |                     |

All the reactions were performed at 1 mmol scale at room temperature in water by stirring the reaction mixture for the proper time, otherwise mentioned; <sup>a</sup>mediated by tin at 80°C; <sup>b</sup>promoted by sonication; <sup>c</sup>mediated by zinc with sonication; <sup>d</sup>by <sup>1</sup>Hnmr.

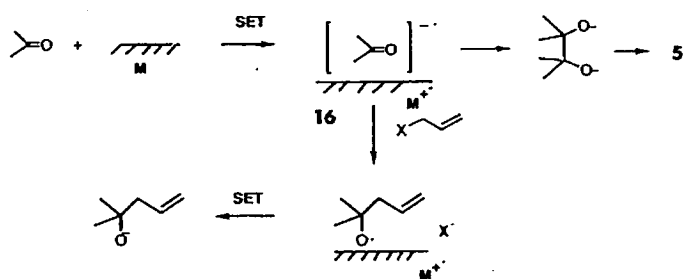
So far, the most commonly used metal in aqueous organometallic reaction are zinc and tin.

Very often, acid catalysts, heat or sonication are required to induce the reaction to occur.

⊙ Reactions with indium metal need no promoter.

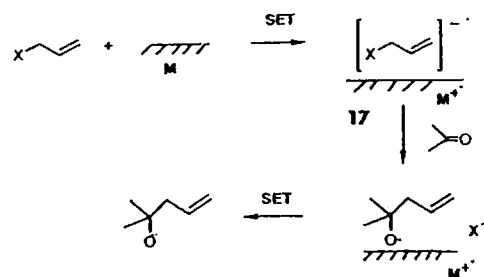
The use of indium generally improved the yields (entries 3 and 4, 10-14)

Proposed Mechanism (Can. J. Chem. 1994, 72, 1181.)



This mechanism can account not only for the product but also for the side product of the namely the pinacol 5.

Another equally likely mechanism is the following.



In support of this mechanism, the self-coupling product of the allylic halide can also be found in the reaction mixture as a side product.

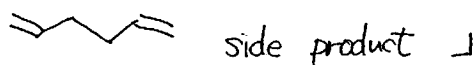


Table I. First to Fourth Ionization Potential of Some Metals

| Metal     | Ionization Potential (eV) |        |        |        |
|-----------|---------------------------|--------|--------|--------|
|           | I                         | II     | III    | IV     |
| Indium    | 5.785                     | 18.86  | 28.03  | 54.4   |
| Aluminium | 5.984                     | 18.82  | 28.44  | 119.96 |
| Magnesium | 7.646                     | 15.035 | 80.143 | 109.29 |
| Zinc      | 9.39                      | 17.96  | 39.7   |        |
| Tin       | 7.34                      | 14.63  | 30.49  | 40.72  |

If aqueous organometallic reactions proceed by a single electron transfer mechanism, indium may well be effective in such reactions.

#### Unexpected Barbier-Grignard Allylation of Aldehydes with Magnesium in Water

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J. Am. Chem. Soc. 1988, 110, 9102.

J. Org. Chem. 1999, 64, 3230.

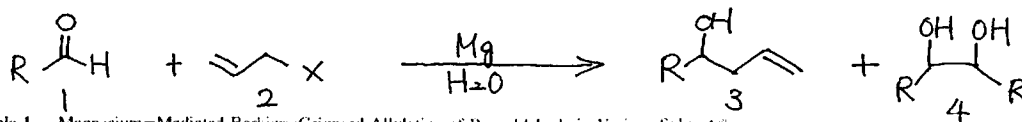


Table 1. Magnesium-Mediated Barbier-Grignard Allylation of Benzaldehyde in Various Solvents<sup>a</sup>

| entry | allyl halide  | solvent                        | mediator          | 3/4/benzyl alcohol | conversion (%) of aldehyde |
|-------|---------------|--------------------------------|-------------------|--------------------|----------------------------|
| 1     | allyl bromide | THF/H <sub>2</sub> O (10:0.04) | Mg/I <sub>2</sub> | 100%/0/0           | quantitative               |
| 2     | allyl bromide | THF/H <sub>2</sub> O (10:0.2)  | Mg/I <sub>2</sub> | 100%/0/0           | quantitative               |
| 3     | allyl bromide | THF/H <sub>2</sub> O (10:0.55) | Mg/I <sub>2</sub> | 98%/0/0            | 98                         |
| 4     | allyl bromide | THF/H <sub>2</sub> O (10:0.67) | Mg/I <sub>2</sub> | 9%/43%/4%          | 56                         |
| 5     | allyl bromide | THF/H <sub>2</sub> O (10:0.7)  | Mg/I <sub>2</sub> | 0/0/0              | 0                          |
| 6     | allyl bromide | H <sub>2</sub> O               | Mg/I <sub>2</sub> | 13%/2%/1%          | 16                         |
| 7     | allyl bromide | 0.1 N HCl                      | Mg/I <sub>2</sub> | 28%/66%/6%         | quantitative               |
| 8     | allyl bromide | 0.1 N NH <sub>4</sub> Cl       | Mg                | 41%/52%/7%         | quantitative               |
| 9     | allyl iodide  | 0.1 N NH <sub>4</sub> Cl       | Mg                | 58%/34%/18%        | quantitative               |

<sup>a</sup> Entries 1-6: benzaldehyde:allyl halide:magnesium = 1:3:20. Entries 7-9: benzaldehyde:allyl halide:magnesium = 1:3:10 (the use of a stoichiometric amount of magnesium resulted in a low conversion).

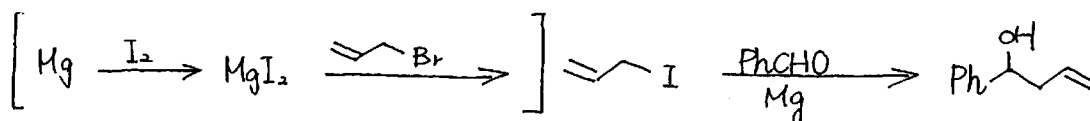


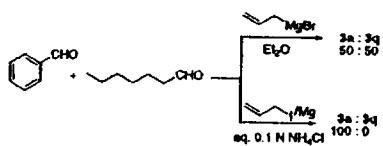
Table 2. Alkylation Reaction Mediated by Magnesium in Aqueous Medium

| entry | substrate (1) | yield (3, %) <sup>a</sup> | yield (4, %) <sup>a,b</sup> | yield (11, %) <sup>a</sup> | entry | substrate (1) | yield (3, %) <sup>a</sup> | yield (4, %) <sup>a,b</sup> | yield (11, %) <sup>a</sup> |
|-------|---------------|---------------------------|-----------------------------|----------------------------|-------|---------------|---------------------------|-----------------------------|----------------------------|
| 1     |               | 50(50)                    | 34                          | 8                          | 10    |               | 47(40)                    | 38                          | 5                          |
| 2     |               | 57(50)                    | 36                          | 7                          | 11    |               | 30(21)                    | 54                          | 18                         |
| 3     |               | 52(45)                    | 36                          | 12                         | 12    |               | 45(40)                    | 37                          | 18                         |
| 4     |               | 53(43)                    | 35                          | 12                         | 13    |               | 27(10)                    | 52                          | 21                         |
| 5     |               | 42(35)                    | 63                          | 5                          | 14    |               | 3                         | 2                           | 95(90)                     |
| 6     |               | 42(34)                    | 37                          | 21                         | 15    |               | 0                         | 0                           | 0                          |
| 7     |               | 40(32)                    | 47                          | 13                         | 16    |               | 0                         | 0                           | 0                          |
| 8     |               | 39(30)                    | 54                          | 7                          | 17    |               | 0                         | 0                           | 0                          |
| 9     |               | 53(45)                    | 33                          | 14                         | 18    |               | 0                         | 0                           | 0                          |

Reactions were carried out by using aldehyde: silyl iodide: magnesium turning (1:3:10) in 0.1 N aqueous NH<sub>4</sub>Cl. <sup>a</sup>Measured by <sup>1</sup>H NMR (isolated yields in parentheses). <sup>b</sup>The total yields of threo and erythro isomers. For entry 15, a polymeric product was obtained.

The reduction potential of aldehydes are affected by many factors.

Under similar conditions, the half wave reduction potentials of aliphatic aldehydes are more negative than those of aromatic aldehyde.



for example: (現代電気化学入門)

CH<sub>3</sub>CHO (EtOH, pH = 8, E<sub>1/2</sub> = -1.7 eV)

Ph CHO (EtOH, pH = 8, E<sub>1/2</sub> = -1.4 eV)

The Barbier-Grignard-Type Carbonyl Alkylation Using Unactivated Alkyl Halides in Water

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Scheme 1

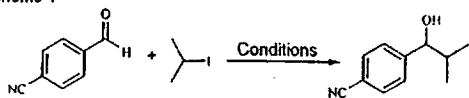


Table 1. Optimization Conditions

| entry | conditions <sup>a</sup> | solvent  | yield (%) <sup>b</sup> |
|-------|-------------------------|--|------------------------|
| 1     | InCl/Zn                 | H <sub>2</sub> O                                     | 0                      |
| 2     | InCl/TBDMSCl/Zn/CuBr    | H <sub>2</sub> O                                     | 30 <sup>c</sup>        |
| 3     | InCl/Zn/CuI             | H <sub>2</sub> O                                     | 13:33:54               |
| 4     | Zn/CuI                  | H <sub>2</sub> O                                     | 0:38:62                |
| 5     | InCl/CuBr               | H <sub>2</sub> O                                     | no reaction            |
| 6     | InCl/CuI                | H <sub>2</sub> O                                     | no reaction            |
| 7     | InCl/Zn/CuI             | 0.07 M Na <sub>2</sub> C <sub>2</sub> O <sub>4</sub> | 0:12:88 <sup>d</sup>   |
| 8     | InCl/CuBr               | 0.07 M Na <sub>2</sub> C <sub>2</sub> O <sub>4</sub> | no reaction            |
| 9     | InCl/Zn/CuI             | 0.07 M K <sub>2</sub> C <sub>2</sub> O <sub>4</sub>  | 0:25:75                |
| 10    | InCl/Zn/CuI             | 0.07 M KOAc  | 0:36:64                |
| 11    | InCl/Zn/CuI             | 0.05 M Na <sub>2</sub> C <sub>2</sub> O <sub>4</sub> | 6:12:82                |
| 12    | InCl/CuI                | 0.05 M Na <sub>2</sub> C <sub>2</sub> O <sub>4</sub> | no reaction            |
| 13    | InCl/Zn                 | 0.05 M Na <sub>2</sub> C <sub>2</sub> O <sub>4</sub> | trace                  |
| 14    | Zn/CuI                  | 0.05 M Na <sub>2</sub> C <sub>2</sub> O <sub>4</sub> | 13:17:71               |

<sup>a</sup> 18 h reaction at room temperature, based upon 20 mg (0.153 mmol) of p-cyanobenzaldehyde. <sup>b</sup> Yield from crude <sup>1</sup>H NMR, ratio of unreacted aldehyde:pinacol:desired product. <sup>c</sup> Isolated yield. <sup>d</sup> 0.10 equiv of InCl, 3 equiv of CuI, 5 equiv of isopropyl iodide, 6 equiv of Zn.

Scheme 2

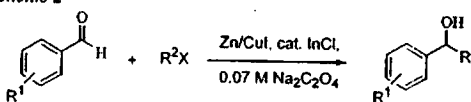


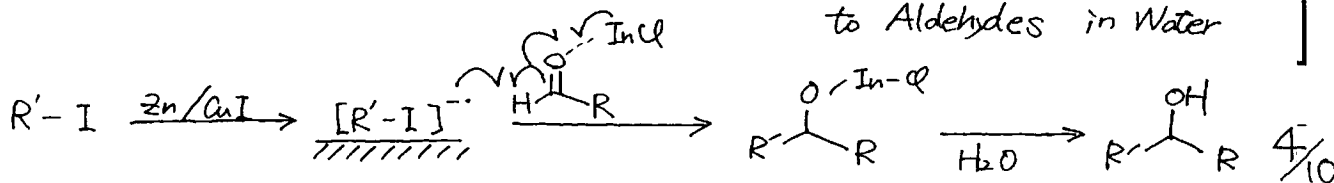
Table 2. Alkylation of Various Aldehydes

| entry | RCHO  | R'X                    | yield (%) <sup>a</sup> |
|-------|---|------------------------|------------------------|
| 1     | 4-CNC <sub>6</sub> H <sub>4</sub> CHO               | cyclohexyl iodide      | 71                     |
| 2     | 4-CNC <sub>6</sub> H <sub>4</sub> CHO               | cyclohexyl bromide     | 41                     |
| 3     | 4-CNC <sub>6</sub> H <sub>4</sub> CHO               | cyclopentyl iodide     | 67                     |
| 4     | 4-CNC <sub>6</sub> H <sub>4</sub> CHO               | isopropyl iodide       | 85                     |
| 5     | 4-CNC <sub>6</sub> H <sub>4</sub> CHO               | tert-butyl iodide      | 30                     |
| 6     | 4-CNC <sub>6</sub> H <sub>4</sub> CHO               | 1-iodo-2-methylpropane | 32                     |
| 7     | 4-CNC <sub>6</sub> H <sub>4</sub> CHO               | 1-iodohexane           | 14                     |
| 8     | 4-BrC <sub>6</sub> H <sub>4</sub> CHO               | cyclohexyl iodide      | 58                     |
| 9     | 4-ClC <sub>6</sub> H <sub>4</sub> CHO               | cyclohexyl iodide      | 53                     |
| 10    | PhCHO   | cyclohexyl iodide      | 46                     |
| 11    | 3-MeC <sub>6</sub> H <sub>4</sub> CHO               | cyclohexyl iodide      | 47                     |
| 12    | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO | isopropyl iodide       | 30                     |
| 13    | 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO | isopropyl iodide       | 83                     |
| 14    | 4-MeOC <sub>6</sub> H <sub>4</sub> CHO              | cyclohexyl iodide      | 56                     |
| 15    | 3-HOC <sub>6</sub> H <sub>4</sub> CHO               | isopropyl iodide       | 47                     |
| 16    | 3-ClC <sub>6</sub> H <sub>4</sub> CHO               | cyclohexyl iodide      | 66                     |

<sup>a</sup> Isolated yields were reported.

- When the reaction was carried out in organic solvents such as THF, methanol and methylene chloride, no desired reaction product was observed.
- No reaction was observed with aliphatic aldehyde and ketones.

Proposed Mechanism for the Metal-Mediated Addition of Alkyl Halides to Aldehydes in Water



## Tin- and Indium-Mediated Allylation in Aqueous Media: Application to Unprotected Carbohydrates

Enoch Kim, Dana M. Gordon, Walther Schmid, and George M. Whitesides\* *J. Org. Chem.* 1993, 58, 5500-5507

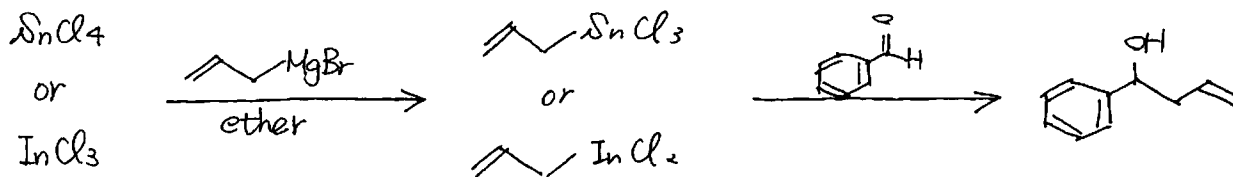


Table III. Summary of Organic Halides and Organometallic Reagents

| A. Organic Halides |                       |              |             |
|--------------------|-----------------------|--------------|-------------|
| successful         | metals (unsuccessful) | unsuccessful | metals used |
|                    | In, Sn, (Zn)          |              | In, Sn      |
|                    | In, Sn*               |              | In, Sn      |
|                    | In, Sn                |              | In, Sn      |
|                    | In, Sn                |              | Sn          |
|                    | In, Sn                |              | In, Sn      |
|                    | In, Sn                |              | In, Sn      |
|                    |                       |              | Sn          |
|                    |                       |              | In, Sn*     |
|                    |                       |              | In, Sn      |

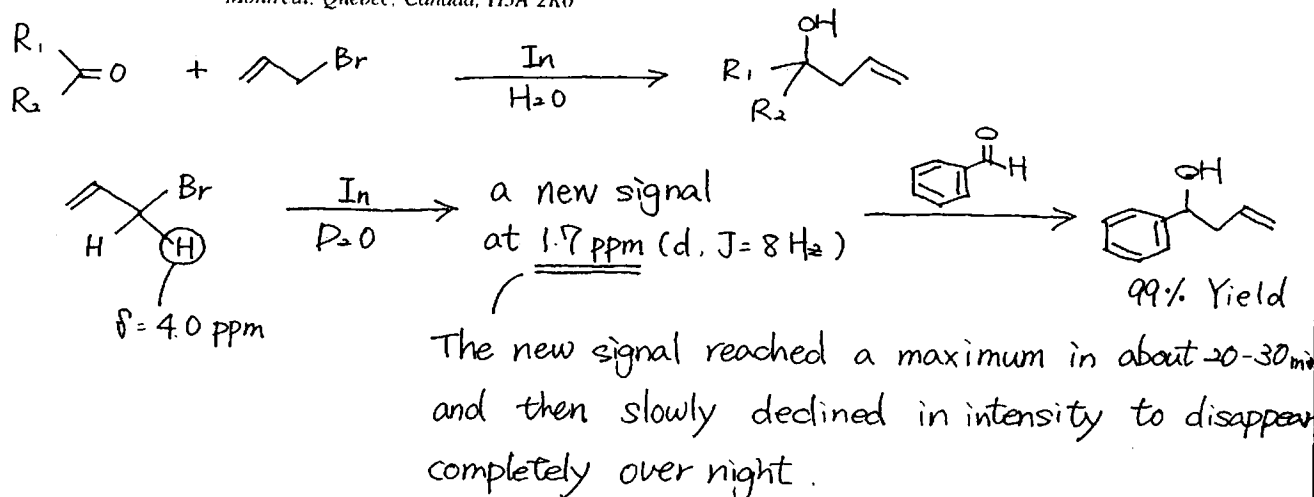
| B. Organometallic Reagents |   |
|----------------------------|---|
| successful                 | unsuccessful  |
|                            |   |
|                            |   |
|                            | <p> <math>\text{MeMgBr}</math>; <math>\text{EtMgBr}</math>/<math>\text{SnCl}_4</math> (THF)<br/> <math>\text{benzylMgCl}</math>/<math>\text{SnCl}_4</math> (THF, ether)<br/> <math>\text{phenylMgBr}</math>; <math>\text{ethylMgBr}</math>/<math>\text{SnCl}_4</math> (THF)<br/> <math>\text{vinylMgBr}</math>/<math>\text{SnCl}_4</math> (THF)<br/> <math>\text{allylMgBr}</math>/<math>\text{SnCl}_4</math> (ether)<br/> <math>\text{TMG}</math>-<math>\text{MgBr}</math>/<math>\text{SnCl}_4</math> (ether)         </p> |

The use of authentic organotin and organoindium reagents gave outcomes essentially identical to those obtained under heterogeneous conditions, implying common reactive species.

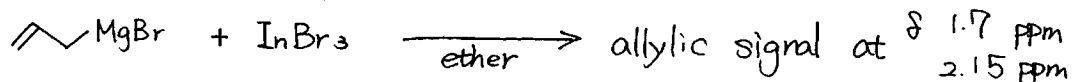
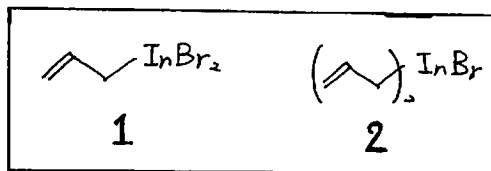
### Indium-Mediated Organometallic Reactions in Aqueous Media: The Nature of the Allylindium Intermediate

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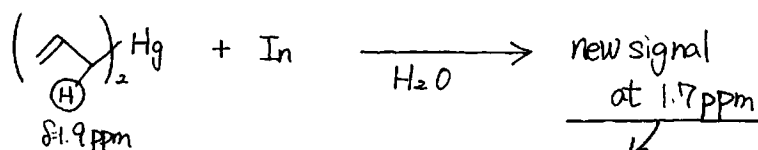
They tried to see if the allylindium intermediate could have either structure **1** or **2**



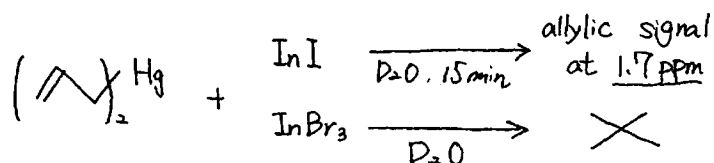
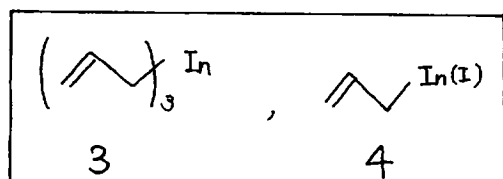
over night → the signal at 1.7 was greatly reduced, and the signal at 2.15 was enhanced.

allylic signal at both  $\delta$  1.7 and 2.15  $\xrightarrow{\text{D}_2\text{O}}$  the signal at 1.7 ppm only

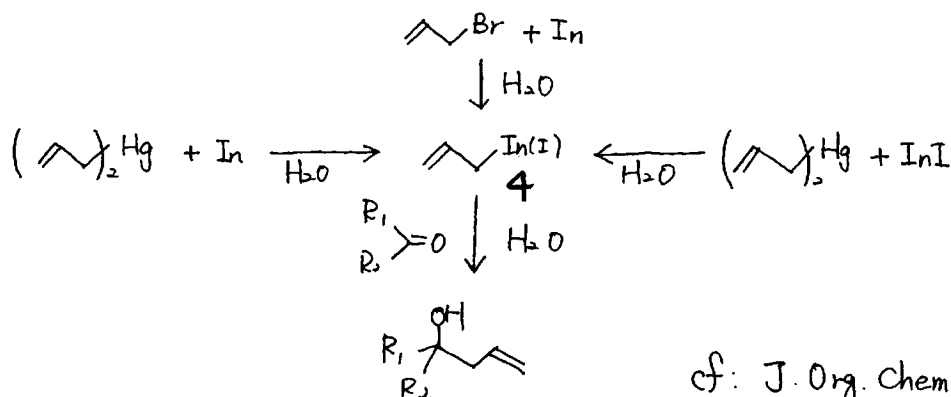
They turned to other methods for the preparation of organoindium compound.



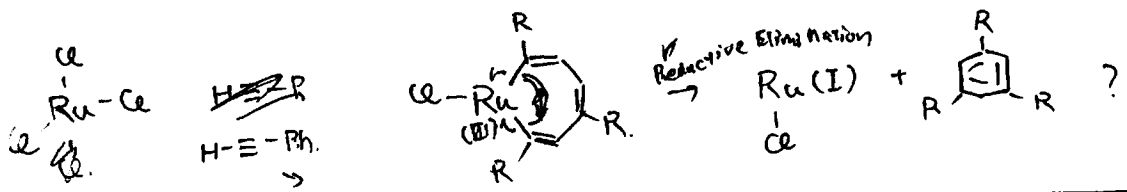
The same transient allylindium species has been formed, and since no bromide was involved in the trans metalation reaction, the allylindium species cannot be **1** or **2** ↓



The transient allylindium species in aqueous media is allylindium(I)



cf: J. Org. Chem., 1999, 64, 4452.



P

**Highly efficient Grignard-type imine additions via C-H activation in water and under solvent-free conditions**

Chao-Jun Li\* and Chunmei Wei

Chem. Commun. 2002, 2440

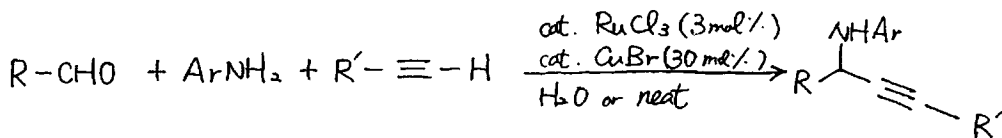
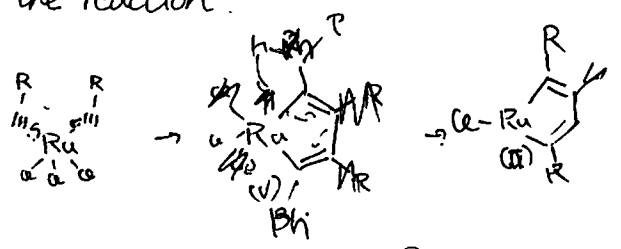


Table 1 Catalytic addition of phenylacetylene to imines in water (or neat)

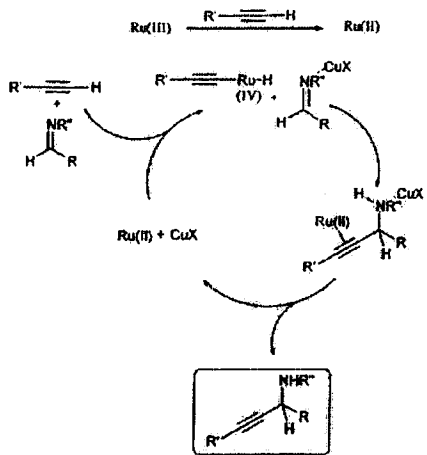
| Entry | Aldehyde | Aniline/conditions   | Product | Yield (%) |
|-------|----------|----------------------|---------|-----------|
| 1     |          | PhNH <sub>2</sub> /A |         | 91        |
| 2     |          | PhNH <sub>2</sub> /A |         | 90        |
| 3     |          | PhNH <sub>2</sub> /A |         | 89        |
| 4     |          | PhNH <sub>2</sub> /A |         | 95        |
| 5     |          | PhNH <sub>2</sub> /A |         | 93        |
| 6     |          | PhNH <sub>2</sub> /A |         | 87        |
| 7     |          | PhNH <sub>2</sub> /A |         | 86        |
| 8     |          | PhNH <sub>2</sub> /A |         | 87        |
| 9     |          | PhNH <sub>2</sub> /A |         | 64        |
| 10    |          | PhNH <sub>2</sub> /B |         | 85        |

conditions<sup>a</sup>: A, in water; B, solvent free

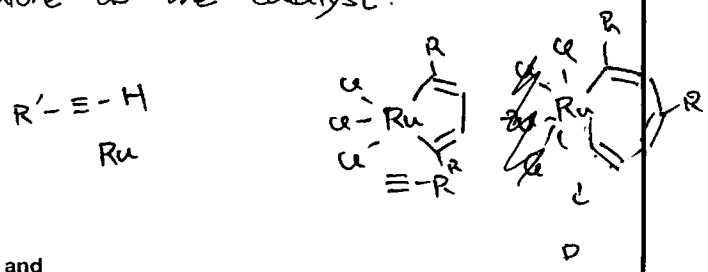
Aliphatic alkynes, such as hexyne and trimethylsilylacetylene, were also effective for the reaction.



**Tentative mechanism for imine addition via C-H activation.**



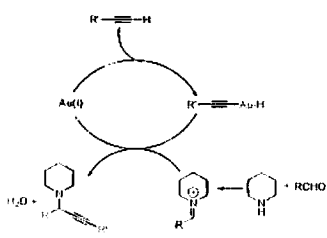
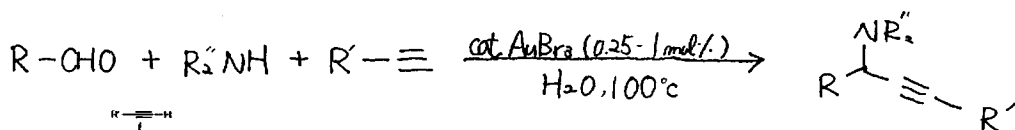
- The conversion was decreased when a smaller amount of CuBr was used.
- No imine addition product was observed with RuCl<sub>3</sub> alone as the catalyst.



**A Highly Efficient Three-Component Coupling of Aldehyde, Alkyne, and Amines via C-H Activation Catalyzed by Gold in Water**

Chunmei Wei and Chao-Jun Li\*

J. Am. Chem. Soc. 2003, 125, 9585.



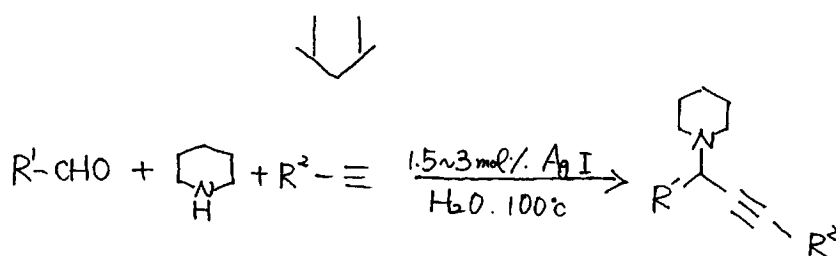
Au(I) can be generated in situ from reduction of Au(III) by the alkyne

Table 2. Coupling of Aldehyde, Alkyne, and Amine Catalyzed by Gold in Water

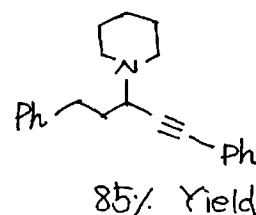
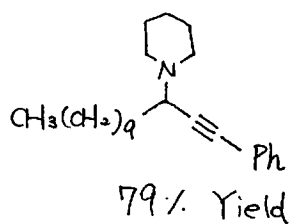
| entry | aldehyde  | amine                  | product | yield <sup>a</sup> |
|-------|---|------------------------|---------|--------------------|
| 1     | PhCHO   | piperidine             |         | >99%               |
| 2     | <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CHO               | piperidine             |         | 87%                |
| 3     | <i>p</i> -EtC <sub>6</sub> H <sub>4</sub> CHO               | piperidine             |         | 95%                |
| 4     | <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CHO              | piperidine             |         | 91%                |
| 5     | <i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO | piperidine             |         | 98% <sup>b</sup>   |
| 6     | <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CHO               | piperidine             |         | >99%               |
| 7     | <i>m</i> -ClC <sub>6</sub> H <sub>4</sub> CHO               | piperidine             |         | >99%               |
| 8     | <i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CHO               | piperidine             |         | >99%               |
| 9     | <i>m</i> -BrC <sub>6</sub> H <sub>4</sub> CHO               | piperidine             |         | >99%               |
| 10    | PhCHO   | HN(allyl) <sub>2</sub> |         | 95%                |
| 11    | PhCHO   | HN(Bn) <sub>2</sub>    |         | 99%                |
| 12    | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> CHO         | piperidine             |         | 53%                |
| 13    | Ph-CHO  | piperidine             |         | 75%                |
| 14    |   | piperidine             |         | 96%                |
| 15    | <i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO | piperidine             |         | >99%               |
| 16    | <i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO | piperidine             |         | >99%               |

<sup>a</sup> Isolated yields based on aldehyde. <sup>b</sup> Reaction was carried out at 70 °C.

The decreased yield for aliphatic aldehydes is caused by the trimerization of aliphatic aldehydes (entry 12 and 13)



Org. Lett. 2003, 5, 4473

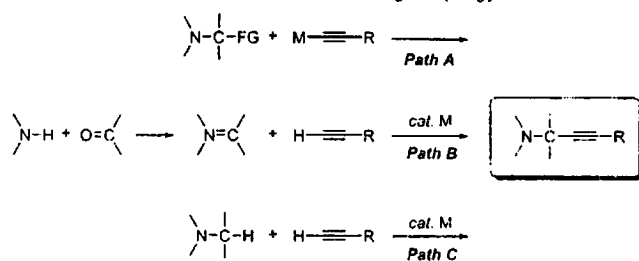


### CuBr-Catalyzed Efficient Alkynylation of sp<sup>3</sup> C-H Bonds Adjacent to a Nitrogen Atom

Zhiping Li and Chao-Jun Li\*

J. Am. Chem. Soc. 2004, 126, 11810

#### Scheme 1. Various Methods for Forming Propargylamines



Path A stands for stoichiometric nucleophilic reaction.

J. Am. Chem. Soc. 2004, 126, 5958

Path B is the transition metal-catalyzed reactions of alkynes and imines.

Table 1. Selection of Copper Catalyst<sup>a</sup>

| entry | catalyst              | NMR yield <sup>b</sup> |
|-------|-----------------------|------------------------|
| 1     | CuBr                  | 77                     |
| 2     | CuBr <sub>2</sub>     | 72                     |
| 3     | CuCl                  | 75                     |
| 4     | CuCl <sub>2</sub>     | 73                     |
| 5     | CuI                   | 56                     |
| 6     | Cu(I) <sub>2</sub> Se | 61                     |
| 7     | CuOTf                 | 15                     |
| 8     | Cu(OTf) <sub>2</sub>  | 3                      |
| 9     | no                    | 0                      |

CuBr and CuCl proved to be the best catalysts.

When the amount of *N,N*-dimethylaniline was reduced, the yields also decreased.

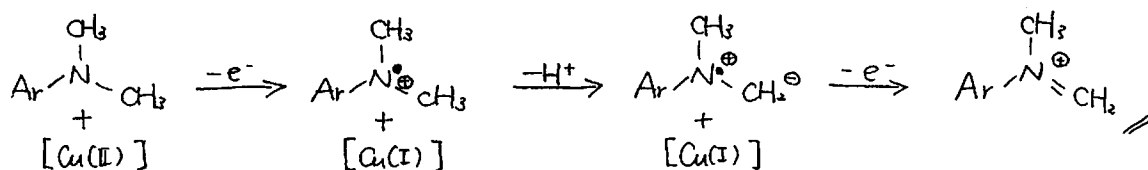
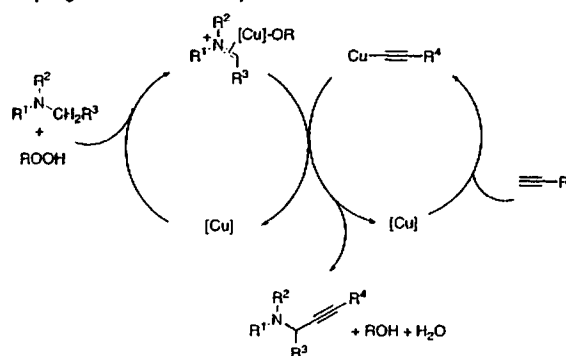


Table 2. Copper-Catalyzed Alkylation of Amines<sup>a</sup>

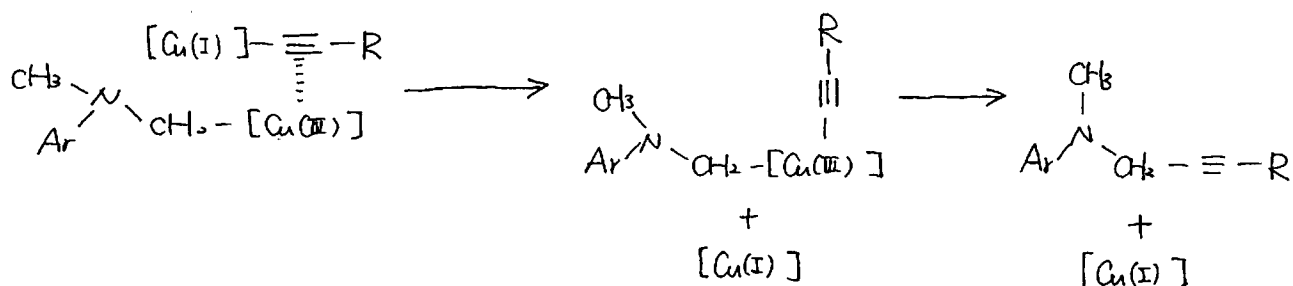
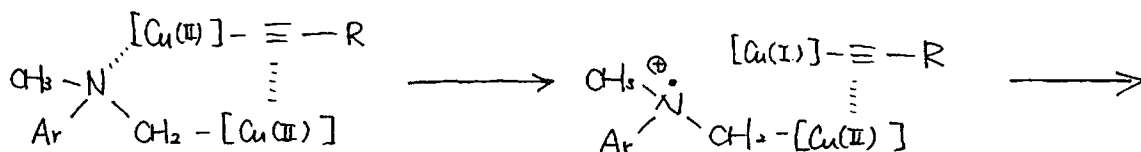
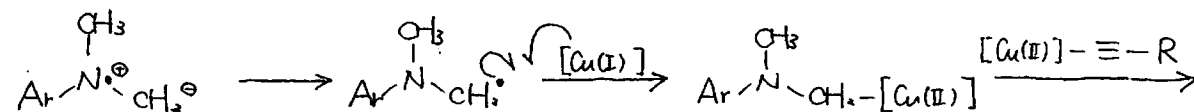
| entry | Ar     | R                    | product | yield <sup>b</sup> |
|-------|--------|----------------------|---------|--------------------|
| 1     | Ph     | Ph                   | 3a      | 74                 |
| 2     | Ph     | 4-MeOPh              | 3b      | 82                 |
| 3     | Ph     | 4-MePh               | 3c      | 74                 |
| 4     | Ph     | 4-BrPh               | 3d      | 74                 |
| 5     | Ph     | 4-PhPh               | 3e      | 60                 |
| 6     | Ph     | 2-Py                 | 3f      | 36                 |
| 7     | Ph     | HOCH <sub>2</sub>    | 3g      | 40                 |
| 8     | Ph     | EtCOOCH <sub>2</sub> | 3h      | 58                 |
| 9     | Ph     | CH <sub>2</sub> OCO  | 3i      | 25                 |
| 10    | Ph     | Bu                   | 3j      | 12                 |
| 11    | 4-MePh | Ph                   | 3k      | 73                 |
| 12    | 2-MePh | Ph                   | 3l      | 53                 |
| 13    | 4-BrPh | Ph                   | 3m      | 69                 |

<sup>a</sup> 4.0 mmol amine, 2.0 mmol alkyne, 0.1 mmol copper bromide, and 0.4 mL <sup>t</sup>BuOOH (5–6 M in decane). <sup>b</sup> Isolated yields were based on alkynes.

Scheme 5. Tentative Mechanism for the Direct Oxidative Coupling of Amine with Alkyne

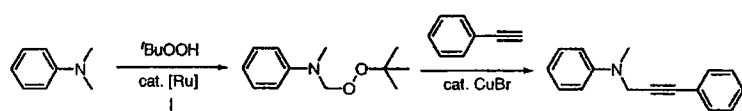


< Another Proposed Mechanism >



J. Chem. Soc. (M), 1993, 2837.  
J. Chem. Soc. (B), 1968, 269.

They also propose



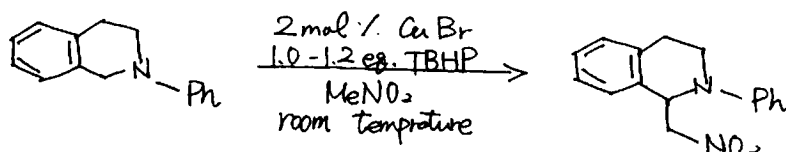
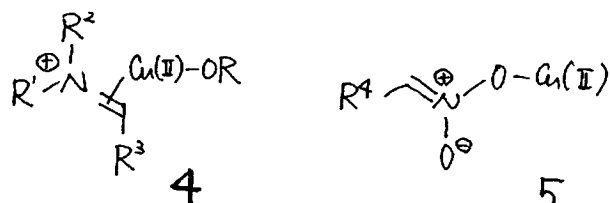
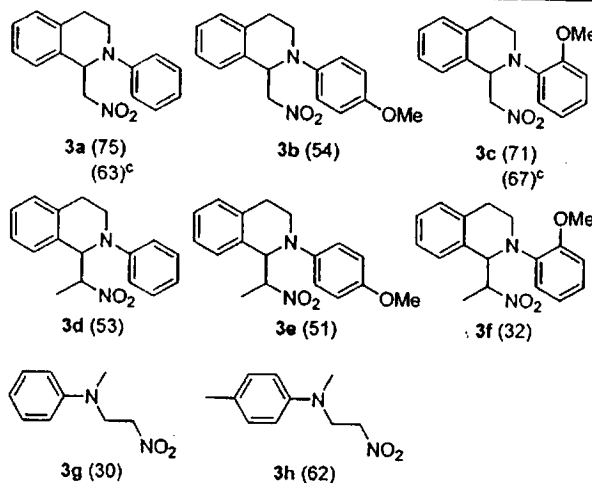
80% → J. Am. Chem. Soc. 1988, 110, 8256

### Highly Efficient Copper-Catalyzed Nitro-Mannich Type Reaction: Cross-Dehydrogenative-Coupling between $sp^3$ C-H Bond and $sp^3$ C-H Bond

Zhiping Li and Chao-Jun Li\*

J. Am. Chem. Soc.

2005, 127, 3672

products (isolated yields %)<sup>a</sup>

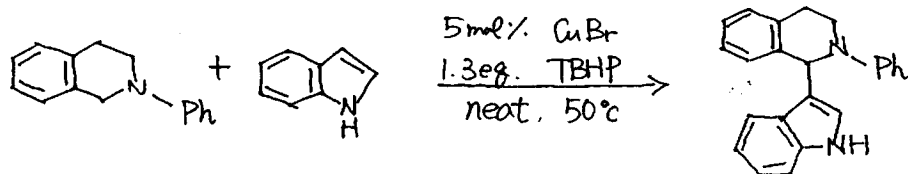
Copper catalyzed the formation of an imine-type intermediate 4 through H-abstraction of  $sp^3$  C-H adjacent to nitrogen.

The copper catalyst also activated the nitroalkanes to form intermediate 5.

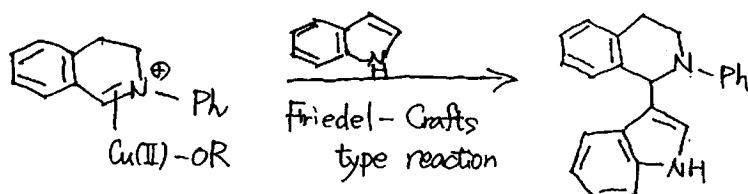
### CuBr-Catalyzed Direct Indolation of Tetrahydroisoquinolines via Cross-Dehydrogenative Coupling between $sp^3$ C-H and $sp^2$ C-H Bonds

Zhiping Li and Chao-Jun Li\*

J. Am. Chem. Soc. ASAP



| entry | 1 | 2 | product | yield (%) <sup>a</sup> |
|-------|---|---|---------|------------------------|
| 1     |   |   |         | 88 (78)                |
| 2     |   |   |         | 89 (57)                |
| 3     |   |   |         | 89 (61)                |
| 4     |   |   |         | 81 (77)                |
| 5     |   |   |         | 77 (63)                |
| 6     |   |   |         | 88 (44)                |
| 7     |   |   |         | 88 (73)                |
| 8     |   |   |         | 85                     |
| 9     |   |   |         | 64 (30)                |
| 10    |   |   |         | 25 (11)                |



The advantages of this method include:

- (1) relatively mild reaction conditions
- (2) use of free (NH) indoles
- (3) tolerance of various functional groups
- (4) high regioselectivity
- (5) use of a relatively cheap metal copper as catalyst.