Decarboxylative $sp^3$ C–N Couplings: Recent Progress

**Outline**

- General considerations
- Decarboxylative $sp^3$ C–N coupling under non-photonic conditions
- Decarboxylative $sp^3$ C–N coupling using bicyclic tertiary acids
- Decarboxylative $sp^3$ C–N coupling using new $N$-heterocycles

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Decarboxylative $sp^3$ C–N Couplings

### General considerations

- Ir
  - Ir(F-Meppy)$_2$(dtbbpy)PF$_6$
    - Strem 77-0320
  - Ir(ppy)$_3$
    - Strem 77-7015

- Cu
  - CuTC
    - CAS 68986-76-5
  - BPhen
    - CAS 1662-01-7
  - dOMe-Phen
    - CAS 92149-07-0

- Organic base
  - BTMG
    - CAS 29166-72-1
  - BTTP
    - CAS 161118-67-8
  - DBU
    - CAS 6674-22-2
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Unpublished Results
**Decarboxylative sp\(^3\) C–N Couplings: Non-Photonic Conditions**

- **Non-photonic conditions: indole scope**

  ![Reaction Scheme]

  - 20 mol% CuTC, 30 mol% **dMe-Phen**
  - 3 equiv BTMG
  - Dioxane (3 mL), r.t., 1 h

  ![Product Structures]

  - **58% yield**
  - **50% yield**
  - **49% yield**
  - **50% yield**
  - **48% yield**
  - **49% yield**

NMR yield
Decarboxylative $sp^3$ C–N Couplings: Non-Photonic Conditions

Non-photonic conditions: 7-azaindole scope, with BTMG

```
R

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{OCOCy} & \quad \text{Me} \quad \text{OCOCy} \\
\text{Mes} & \quad \text{Me} \\
\end{align*}
\]

20 mol% CuTC, 30 mol% Me$_4$-Phen
2 equiv BTMG
dioxane (3 mL), r.t., 1 h

\[
\begin{align*}
\text{R} & \quad \text{N} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

1 equiv 0.1 mmol
2 equiv

```

NMR yield

75% yield
82% yield
94% yield
85% yield
59% yield
52% yield
Decarboxylative \( sp^3 \) C–N Couplings: Non-Photonic Conditions

Non-photonic conditions: 7-azaindole scope, with DBU

\[
\begin{align*}
\text{Re} & \quad \text{OCOCy} \\
\text{Me} & \quad \text{OCOCy} \\
\text{R} & \quad \\
\text{N} & \quad \\
\text{N} & \quad \\
\text{N} & \quad \\
\text{N} & \quad \\
\text{N} & \quad \\
\text{N} & \quad \\
\end{align*}
\]

20 mol\% CuTC, 30 mol\% \text{Me}_4\text{-Phen}  
4 equiv DBU  
dioxane (3 mL), r.t., 1 h

\[
\begin{align*}
\text{Cl} & \quad \text{Br} \\
\text{Cl} & \quad \text{Br} \\
\text{Cl} & \quad \\
\text{NC} & \quad \\
\end{align*}
\]

\begin{align*}
69\% \text{ yield} & \quad 67\% \text{ yield} & \quad 92\% \text{ yield} \\
71\% \text{ yield} & \quad 57\% \text{ yield} & \quad 60\% \text{ yield}
\end{align*}

NMR yield

\text{Me}_4\text{-Phen}
Decarboxylative sp$^3$ C–N Couplings: Non-Photonic Conditions

Non-photonic conditions: pyrazole scope

\[
\text{Pyrazole} \quad \text{Mes} \quad \text{OCOCy} \quad \text{OCOCy} \quad \text{CuTC, BPhen} \quad \text{dioxane, r.t., 1 h}
\]

1 equiv 0.1 mmol 2 equiv

95% yield 94% yield 82% yield 65% yield

97% yield 91% yield 61% yield

Ar = para-Cl-C$_6$H$_4$ Ar = para-Br-C$_6$H$_4$
Decarboxylative $sp^3$ C–N Couplings: Non-Photonic Conditions

Non-photonic conditions: other $N$-heterocycles scope

1 equiv 0.1 mmol

2 equiv

40 mol% CuTC, 60 mol% BPhen no exogenous base
dioxane (3 mL), r.t., 1 h

single regioisomer

73% yield

48% yield

34% yield

82% yield

85% yield
Decarboxylative sp$^3$ C–N Couplings: Non-Photonic Conditions

Non-photonic conditions: experimental procedure

**Procedure:**
To an 8 mL vial equipped with a stir bar was added $N$-nucleophile, copper salt, ligand, and iodomesitylene dicarboxylate. Dioxane was added and the solution was degassed *immediately* by sparging with $N_2$ for 3–5 minutes. If necessary, exogenous base (such as BTMG or DBU) was added under the atmosphere of $N_2$. The reaction was stirred for 1 hour at room temperature. An internal standard (mesitylene) was added and the crude reaction mixture was analyzed by $^1$H NMR.

**Notes:**
1. If the iodomesitylene dicarboxylate or the $N$-nucleophile is a liquid, its solution in dioxane was used instead.
2. Pre-mixing the copper salt and the ligand in solution is not necessary. If a stock solution of copper catalyst is needed, the ligation step (such as stirring or sonification the solution) should be performed under the atmosphere of $N_2$. 

\[ \text{1 equiv } 0.1 \text{ mmol} \quad 2 \text{ equiv} \]

```
Cl
Mes-\text{OCOCy}
N
OCOCy

20 \text{ mol\%} \text{ CuTC}, 30 \text{ mol\%} \text{ Me}_4\text{-Phen}
2 \text{ equiv BTMG}

dioxane (3 mL), r.t., 1 \text{ h}
```

75\% NMR yield
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*Unpublished Results*
Decarboxylative $sp^3$ C–N Couplings: Bicyclic Tertiary Acids

Bicyclo[1.1.1]pentane acid: 7-azaindole scope, non-photonic

- 60 mol% CuTC, 90 mol% Me$_4$-Phen
  - 4 equiv DBU
  - Dioxane (1.5 mL), r.t., 1 h

**Examples:**
- 7-azaindole, scope, non-photonic
  - 49% yield
  - 54% yield
  - 40% yield
  - 45% yield
  - 35% yield
  - 55% yield

NMR yield
Decarboxylative sp³ C–N Couplings: Bicyclic Tertiary Acids

Bicyclo[1.1.1]pentane acid: indole scope, non-photonic

\[
\text{CuTC} \quad 60 \text{ mol\%} \quad \text{BPhen} \quad 90 \text{ mol\%} \quad \text{DBU} \quad 4 \text{ equiv} \quad \text{dioxane (1.5 mL), r.t., 1 h}
\]

1 equiv \quad 1 equiv \quad 0.05 \text{ mmol}

46% yield \quad 47% yield \quad 61% yield \quad 54% yield

52% yield \quad 52% yield \quad 58% yield

NMR yield
Decarboxylative sp$^3$ C–N Couplings: Bicyclic Tertiary Acids

Bicyclo[1.1.1]pentane acid: other N-heterocycles, non-photonic

1 equiv
0.05 mmol

60 mol% CuTC
90 mol% BPhen + 60 mol% H-acac
60 mol% DBU
dioxane (1.5 mL), r.t., 1 h

42% yield
42% yield
63% yield
26% yield
24% yield

H-acac

NMR yield
Decarboxylative sp$^3$ C–N Couplings: Bicyclic Tertiary Acids

Bicyclo[1.1.1]pentane acid: aniline, photoredox

2 mol% Ir(F-Meppy)$_2$(dtbbpy)PF$_6$
60 mol% CuTC, 90 mol% diketone
2 equiv BTTP
dioxane (1.0 mL)
blue LEDs, fan, r.t., 1 h

2 equiv
0.05 mmol

NMR yield

94% yield

92% yield

29% yield

33% yield

diketone
CAS 39207-65-3
Decarboxylative $sp^3$ C–N Couplings: Bicyclic Tertiary Acids

- Bicyclo[2.2.2]octane acid: pyrazole, non-photonic

$$\text{R} \quad \text{Mes} \quad \text{OCOR}$$

1 equiv 2 equiv

0.05 mmol 1 equiv 2 equiv

60 mol% CuTC
no exogenous ligand
no exogenous base
dioxane (1.5 mL), r.t., 1 h

60% yield 56% yield 50% yield 40% yield

NMR yield
Decarboxylative sp$^3$ C–N Couplings: Bicyclic Tertiary Acids

Bicyclo[2.2.2]octane acid: aniline, photoredox

\[
\text{Mes} \quad \text{OCOR} \quad \text{OCOR}
\]

2 mol\% Ir(F-Meppy)$_2$(dtbbpy)PF$_6$
60 mol\% CuTC, 90 mol\% diketone
2 equiv BTTP

2 equiv

\[
\text{dioxane (1.0 mL)}
\]
blue LEDs, fan, r.t., 1 h

\[
\begin{align*}
\text{Br} & \quad n\text{-pentyl} & \text{62\% yield} \\
\text{CN} & \quad n\text{-pentyl} & \text{46\% yield} \\
\text{Cl} & \quad n\text{-pentyl} & \text{85\% yield} \\
F_3C & \quad n\text{-pentyl} & \text{72\% yield} \\
F_3C & \quad n\text{-pentyl} & \text{54\% yield}
\end{align*}
\]

NMR yield

diketone
CAS 39207-65-3
Decarboxylative $sp^3$ C–N Couplings: Bicyclic Tertiary Acids

Bicyclo[2.2.2]octane acid: aniline, photoredox

![Chemical structure](image)

$2 \text{ mol}\% \text{Ir(F-Meppy)}_2(dtbbpy)\text{PF}_6$

$60 \text{ mol}\% \text{CuTC}, 90 \text{ mol}\%$ diketone

$2 \text{ equiv}$ BTTP

Diketone: $\text{Mes} - \text{OCOR} - \text{OCOR}$

$dioxane (1.0 \text{ mL})$

blue LEDs, fan, r.t., 1 h

$1 \text{ equiv}$

$0.05 \text{ mmol}$

$2 \text{ equiv}$

**Yields:**

- 44% yield
- 40% yield
- 60% yield
- 62% yield
- 77% yield

NMR yield

**CAS:** 39207-65-3
Experimental procedure: photoredox conditions

**Procedure:**
To an 8 mL vial equipped with a stir bar was added photocatalyst, N-nucleophile, copper salt, ligand, and iodomesitylene dicarboxylate. Dioxane was added and then base was added to the mixture. Next, the solution was degassed by sparging with N₂ for 3–5 minutes. The reaction was stirred and irradiated using 34 W blue LED lamps (3 cm away, with cooling fan to keep the reaction at room temperature) for 1 hour. An internal standard (mesitylene) was added and the crude reaction mixture was analyzed by ¹H NMR.

**Notes:**
1. If the iodomesitylene dicarboxylate or the N-nucleophile or the ligand is a liquid, its solution in dioxane was used instead.
**Decarboxylative \( sp^3 \) C–N Couplings: Bicyclic Tertiary Acids**

Experimental procedure: non-photonic conditions

![Chemical structures and reaction scheme]

**Procedure:**
To an 8 mL vial equipped with a stir bar was added \( N \)-nucleophile, copper salt, ligand, and iodomesitylene dicarboxylate. Dioxane was added and the solution was degassed *immediately* by sparging with \( \text{N}_2 \) for 3–5 minutes. If necessary, exogenous base (such as BTMG or DBU) was added under the atmosphere of \( \text{N}_2 \). The reaction was stirred for 1 hour at room temperature. An internal standard (mesitylene) was added and the crude reaction mixture was analyzed by \( ^1\text{H} \) NMR.

**Notes:**
1. If the iodomesitylene dicarboxylate or the \( N \)-nucleophile is a liquid, its solution in dioxane was used instead.
2. Pre-mixing the copper salt and the ligand in solution is not necessary. If a stock solution of copper catalyst is needed, the ligation step (such as stirring or sonification the solution) should be performed under the atmosphere of \( \text{N}_2 \).
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Unpublished Results
Decarboxylative $sp^3$ C–N Couplings: New N-Heterocycles

New N-heterocycles: summary of results

![Chemical structures and yields](attachment:chemical_structures.png)
Decarboxylative $sp^3$ C–N Couplings: New N-Heterocycles

New N-heterocycles: summary of conditions

1 mol% photocatalyst
20 mol% CuTC, 30 mol% ligand
2 equiv base

NMR yield
**Decarboxylative \( sp^3 \) C–N Couplings: New N-Heterocycles**

**Experimental procedure: photoredox conditions**

![Chemical structure](image)

**Procedure:**
To an 8 mL vial equipped with a stir bar was added photocatalyst, \( N \)-nucleophile, copper salt, ligand, and iodomesitylene dicarboxylate. Dioxane was added and then base was added to the mixture. Next, the solution was degassed by sparging with \( \text{N}_2 \) for 3–5 minutes. The reaction was stirred and irradiated using 34 W blue LED lamps (3 cm away, with cooling fan to keep the reaction at room temperature) for 1 hour. An internal standard (mesitylene) was added and the crude reaction mixture was analyzed by \(^1\text{H} \) NMR.

**Notes:**
1. If the iodomesitylene dicarboxylate or the \( N \)-nucleophile is a liquid, its solution in dioxane was used instead.