Supplemental information

Chemo- and regioselective benzylic C(sp$^3$)–H oxidation bridging the gap between hetero- and homogeneous copper catalysis

Shantanu Nandi, Shuvam Mondal, and Ranjan Jana
Scheme S1. Preparation of ethyl esters of 2-iodo/bromo benzoic acids or salicylic acids, related to STAR Methods

Scheme S2. Preparation of methyl 2-(((trifluoromethyl)sulfonyl)oxy)benzoate from methyl salicylates, related to STAR Methods

Scheme S3. Suzuki coupling between 2-alkyl aryl boronic acid and 2-iodo/bromo benzoate or methyl 2-(((trifluoromethyl)sulfonyl)oxy)benzoate, related to STAR Methods

Scheme S4. Hydrolysis of methyl esters, related to STAR Methods

Scheme S5. Total synthesis of Alterlactone 21, related to Scheme 5
Scheme S6. Synthesis of Dibenzo[c,e]oxepan-5-thione (DOT, 19), related to Scheme 6

Scheme S7. Synthesis of 2'-((hydroxymethyl)-[1,1'-biphenyl]-2-carboxylic acid (20), related to Scheme 6

Scheme S8. Intramolecular benzylic C-H oxidation of 2'-methyl-[1,1'-biphenyl]-2-carboxylic acid in copper bottle without any external catalyst, related to Scheme 6
Scheme S9. Copper-catalyzed chemo- and regioselective intramolecular benzylic C–H oxidation of 2'-methyl-[1,1'-biphenyl]-2-carboxylic acid 1a in gram-scale, related to Scheme 6.

Scheme S10. Radical quenching experiment, related to Scheme 8.

Scheme S11. Competitive experiment between C(sp²)–H and C(sp³)–H activation, related to Scheme 8.
Scheme S12. Addition of external substituted benzoic acids, related to Scheme 8
Scheme S13. Lactonization reaction of 20 under condition B, related to STAR methods

Scheme S14. Proposed mechanism of double benzylic C(sp^3)-H activation, related to Scheme 9

Table S1. Optimization of condition A, related to Table 1
| Entry | Catalyst Loading [mol%] | Ligand Loading (mol%) | Oxidant (equiv.) | Additive (mol%) | Solvent | Ratio 2a/3a |
|-------|--------------------------|----------------------|------------------|----------------|---------|------------|
| 1     | CuI (20)                 | -                    | DTBP (2)         | -              | DCE     | 52/25      |
| 2     | CuI (20)                 | -                    | DTBP (2)         | -              | PhCl    | 60/27      |
| 3     | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | -              | MeCN    | 48/25      |
| 4     | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | -              | Benzene | 25/45      |
| 5     | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | -              | DMSO    | 5/10       |
| 6     | CuI (20)                 | 1,10-Phen (30)       | O₂               | -              | DMSO    | trace/0    |
| 7     | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | -              | HFIP    | 10/25      |
| 8     | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | -              | DCE     | 55/30      |
| 9     | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | -              | EtOAc   | trace/5    |
| 10    | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | -              | DMF     | ND/27      |
| 11    | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | -              | 1,4- dioxane | ND/5    |
| 12    | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | -              | PhCN    | ND/60      |
| 13    | Cu(OAc)₂·H₂O             | -                    | DTBP (2)         | -              | DCE     | 20/35      |
| 14 a  | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | -              | DCE     | 30/35      |
| 15 b  | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | -              | DCE     | 35/32      |
| 16    | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | HAuCl₄ (5)     | DCE     | 40/32      |
| 17    | CuI (20)                 | 1,10-Phen (30)       | DTBP (2)         | Ag₂CO₃ (40)    | DCE     | ND/32      |
| 18    | CuI (20)                 | Neocuproine (30)     | DTBP (2)         | -              | DCE     | 48/36      |
| 19    | Cu₂O (20)                | 1,10-Phen (30)       | DTBP (2)         | -              | DCE     | 10/42      |
| 20    | CuCl(20)                 | 1,10-Phen (30)       | DTBP (2)         | -              | DCE     | 35/30      |
| 21    | [Cu(MeCN)₄]OTf(20)       | 1,10-Phen (30)       | DTBP (2)         | -              | DCE     | 22/38      |
| No. | Cu Source | Ligand 1 | Ligand 2 | Oxidant | Solvent | Temp. |
|-----|-----------|----------|----------|---------|---------|-------|
| 22  | CuTC (20) | 1,10-Phen (30) | DTBP (2) | - | DCE | 32/28 |
| 23  | [Cu(MeCN)$_n$]PF$_6$ (20) | 1,10-Phen (30) | DTBP (2) | - | DCE | 20/30 |
| 24  | CuOAc (20) | 1,10-Phen (30) | DTBP (2) | - | DCE | 10/30 |
| 25  | CuBr (20) | 1,10-Phen (30) | DTBP (2) | - | DCE | 32/35 |
| 26  | Cul (20) | 1,10-Phen (30) | K$_2$S$_2$O$_8$ (2) | - | DCE | ND/ND |
| 27  | AgNO$_3$ (20) | - | K$_2$S$_2$O$_8$ (2) | - | DCE | ND/ND |
| 28  | Cul (20) | 1,10-Phen (30) | Oxone (2) | - | DCE | ND/ND |
| 29  | Cul (20) | 1,10-Phen (30) | NFSI (2) | - | DCE | ND/ND |
| 30  | Cul (20) | IPr-HCl (30) | DTBP (2) | - | DCE | 20/25 |
| 31  | Cul (20) | 1,10-Phen (30) | DTBP (2) | DBU (200) | DCE | 30/25 |
| 32  | Cul (200) | 1,10-Phen (30) | DTBP (2) | - | DCE | ND/68 |
| 33  | Cul (20) | 1,10-Phen (30) | BPO (2) | - | DCE | 15/ND |
| 34  | Cul (20) | 1,10-Phen (30) | TBHP (2) | - | DCE | 38/33 |
| 35  | Cul (20) | 1,10-Phen (30) | TBPB (2) | - | DCE | 38/20 |
| 36  | Cul (20) | 1,10-Phen (30) | DTBP (2) | NaO'Bu (110) | DCE | trace/15 |
| 37  | Cul (20) | Pyridine (30) | DTBP (2) | - | DCE | 27/40 |
| 38  | Cul (20) | BPY (30) | DTBP (2) | - | DCE | 25/35 |
| 39  | Cul (20) | Terpyridine (30) | DTBP (2) | - | DCE | 13/30 |
| 40  | Cul (20) | X-Phos (30) | DTBP (2) | - | DCE | Trace/45 |
| 41  | Cul (20) | Xantphos (30) | DTBP (2) | - | DCE | Trace/30 |
| 42  | Cul (20) | 1,10-Phen (30) | DTBP (2) | - | PhCF$_3$ | 61/28 |
| 43  | Cul (20) | 1,10-Phen (30) | DTBP (2) | - | THF | 25/38 |
| 44  | Cul (20) | - | DTBP (2) | - | PhCF$_3$ | 65/20 |
| 45  | Cu(OAc)$_2$ (20) | - | DTBP (2) | - | PhCF$_3$ | 46/35 |
| 46  | Cu(OTf)$_2$ (20) | - | DTBP (2) | - | PhCF$_3$ | 42/32 |
|   | Reactant 1    | Reactant 2 | Initiator | Product |
|---|---------------|------------|-----------|---------|
| 47 | CuO(20)      | -          | DTBP (2)  | PhCF<sub>3</sub> | 35/40 |
| 48 | CuI(20)      | -          | TBHP (2)  | PhCF<sub>3</sub> | 40/38 |
| 49 | CuI(20)      | -          | BPO (2)   | PhCF<sub>3</sub> | 20/0  |
| 50 | CuI(20)      | -          | TBPB (2)  | PhCF<sub>3</sub> | 38/20 |
| 51 | CuI (20)     | -          | DTBP (2)  | PhCF<sub>3</sub> | 65/20 |
| 52 | Cu(OAc)<sub>2</sub>(20) | -        | DTBP (2)  | PhCF<sub>3</sub> | 46/35 |
| 53 | CuNP (20)    | -          | DTBP (2)  | PhCF<sub>3</sub> | 80/18 |
| 54 | Cu (20)      | -          | DTBP (2)  | PhCF<sub>3</sub> | 82/12 |
| 55 | Cu (20)      | -          | DTBP (2)  | TEMPO (200) | PhCF<sub>3</sub> | 83/0  |
| 56 | Cu (20)      | -          | DTBP (2)  | BHT (200)   | PhCF<sub>3</sub> | 69/0  |
| 57<sup>a</sup> | Cu (20) | - | DTBP (2) | PhCF<sub>3</sub> | 75/18 |
| 58<sup>b</sup> | Cu (20) | - | DTBP (2) | PhCF<sub>3</sub> | 56/27 |
| 59 | Cu (20)      | 1,10-Phen | DTBP (2)  | PhCF<sub>3</sub> | 70/12 |
| 60 | Cu (20)      | -          | DTBP (2)  | TBAI (120)  | PhCF<sub>3</sub> | 65/12 |
| 61 | Cu (20)      | -          | DTBP (2)  | I<sub>2</sub> (120) | PhCF<sub>3</sub> | 51/12 |
| 62 | Cu (20)      | -          | DTBP (2)  | MnO<sub>2</sub> (200) | PhCF<sub>3</sub> | 60/15 |
| 63 | Cu (20)      | -          | DTBP (2)  | Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O (200) | PhCF<sub>3</sub> | 76/17 |
| 64 | Cu (20)      | -          | DTBP (2)  | MnO<sub>2</sub> (200) | PhCF<sub>3</sub> | 73/8  |
| 65 | Cu (20)      | Yu-auxiliary (30) | DTBP (2) | PhCF<sub>3</sub> | 42/25 |
| 66 | Cu (20)      | -          | DTBP (2)  | Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O (100) | PhCF<sub>3</sub> | 78/15 |
| 67 | Cu (20)      | NMI (30)   | DTBP (2)  | Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O (100) | PhCF<sub>3</sub> | 37/33 |
| 68 | Cu (20)      | 4,4'-DTBPY (30) | DTBP (2) | PhCF<sub>3</sub> | 51/35 |
| 69 | Cu (20)      | Quinox (30) | DTBP (2)  | PhCF<sub>3</sub> | 48/15 |
| 70 | Cu (20)      | -          | DTBP (2)  | BQ (200)   | PhCF<sub>3</sub> | 38/35 |
Table S2. Optimization of condition B, related to Table 1

| Entry | Catalyst Loading [mol%] | Co-catalyst loading (mol%) | Ligand Loading (mol%) | Solvent | Yield of 2a |
|-------|--------------------------|-----------------------------|-----------------------|---------|------------|
| 1     | Cu (20)                  | -                           | -                     | PhCF₃   | 20         |
| 2     | Cu (20)                  | -                           | -                     | MeCN    | 18         |
| 3     | Cu (20)                  | -                           | -                     | DCE     | 18         |
| 4     | Cu (20)                  | -                           | -                     | Benzene | 10         |
| 5     | Cu (20)                  | -                           | -                     | DMSO    | trace      |
| 6     | Cu (20)                  | -                           | -                     | Toluene | 14         |
| 7     | Cul (20)                 | -                           | -                     | PhCF₃   | 15         |
| 8     | Cu(OAc)₂.H₂O (20)        | -                           | -                     | PhCF₃   | 10         |
| 9     | CuO (20)                 | -                           | -                     | PhCF₃   | 10         |
| 10    | [Cu(MeCN)]PF₆ (20)       | -                           | -                     | PhCF₃   | 8          |
| 11    | Cu₂O (20)                | -                           | -                     | PhCF₃   | trace      |
| 12    | Cu(OTf)₂ (20)            | -                           | -                     | PhCF₃   | 10         |
| 13    | Cu (20)                  | -                           | Et₃N (30)             | PhCF₃   | 20         |
| 14    | Cu (20)                  | -                           | Ethylenediamine (30)  | PhCF₃   | ND         |
| 15    | Cu (20)                  | -                           | Pyridine (30)         | PhCF₃   | 10         |
| 16    | Cu (20)                  | -                           | Bpy (30)              | PhCF₃   | Trace      |
| 17    | Cu (20)                  | -                           | Terpyridine (30)      | PhCF₃   | ND         |
| 18    | Cu (20)                  | -                           | TMEDA (30)            | PhCF₃   | 30         |
| 19    | Cu (20)                  | nPrCHO (200)                | -                     | PhCF₃   | 25         |
|   | Cu (20) |     |     |     |     |   |
|---|---------|-----|-----|-----|-----|---|
| 20 | CH₃CHO (200) | -   | PhCF₃ | 22  |
| 21 | PhCHO (200) | -   | PhCF₃ | 18  |
| 22 | ¹PrCHO (200) | -   | PhCF₃ | 22  |
| 23 | nPrCHO (200) | -   | DCE   | 15  |
| 24 | nPrCHO (200) | TMEDA (30) | PhCF₃ | 32  |
| 25 | -       | -   | PhCF₃ | 45  |
| 26 | nPrCHO (200) | TMEDA (30) | PhCF₃ | 37  |
| 27 | nPrCHO (200) | -   | PhCF₃ | 40  |
| 28a | Cu (20) | -   | PhCF₃ | 42  |
| 29a | Cu (20) | Eosin Y (2) | -  | PhCF₃ | 45  |
| 30a | Cu (20) | RB (2) | -  | PhCF₃ | 72  |
| 31a | Cu (20) | Ru(bpy)₂Cl₂ (2) | -  | PhCF₃ | 35   |
| 32a | Cu (20) | Mes-Acr-BF₄ (2) | -  | PhCF₃ | 48   |
| 33a | Cu (20) | RB (2) | TMEDA (30) | PhCF₃ | 50  |
| 34a | Cu (20) | nPrCHO (200)/RB (2) | TMEDA (30) | PhCF₃ | 42  |
| 35a | Cu (20) | nPrCHO (200)/RB (2) | -  | PhCF₃ | 44  |
| 36a,b | Cu (20) | RB (2) | -  | PhCF₃ | 0    |
| 36a,c | Cu (20) | RB (2) | -  | PhCF₃ | 25   |

All reactions were carried out in 0.1 mmol scale. Yields refer to here are overall isolated yields. ¹irradiation from 32W white CFL. ²N₂ environment. ³under air.

**Figure S1.** X-ray determined molecular structure of 2b, **CCDC: 2105616**, related to STAR Methods
Figure S2. X-ray determined molecular structure of 2t, CCDC: 2105617, related to STAR Methods.

Figure S3. Time by time colour of reaction mixture (condition A), related to Figure 2.

Figure S4. UV-VIS absorption spectra of standard reaction with condition A, related to Figure 2.
**Figure S5.** UV-VIS absorption spectra of reaction with condition A excluding 1a and DTBP, related to Figure 2

**Figure S6.** UV-VIS absorption spectra of reaction with condition A excluding 1a, related to Figure 2

**Figure S7.** UV-VIS absorption spectra of standard reaction with condition B, related to Figure 2
Figure S8. UV-VIS absorption spectra of reaction with condition B excluding 1a, related to Figure 2.

Figure S9. UV-VIS absorption spectra of reaction with condition B excluding RB, related to Figure 2.

Figure S10. XPS analysis, related to Figure 2.
**Figure S11.** Turbidity after reactions, related to Figure 2.

**Figure S12.** TEM images after completion of reactions, related to Figure 2.

**Figure S13:** In situ GC data under condition A, related to STAR methods.
Data S1. NMR spectra, related to STAR Methods
$^1$H and $^{13}$C spectra of 2a
$^1$H and $^{13}$C spectra of 2b
$^1$H and $^{13}$C spectra of 2c
$^1$H and $^{13}$C spectra of 2d
$^1$H and $^{13}$C spectra of 2e
$^{1}H$ and $^{13}C$ spectra of 2f
$^1$H and $^{13}$C spectra of 2g
$^1$H and $^{13}$C spectra of 2h
$^{1}$H and $^{13}$C spectra of 2i
$\mathrm{H}$ and $\mathrm{C}^{13}$ spectra of $2j$

$\mathrm{H}$ and $\mathrm{C}^{13}$ spectra of $2j$
$^{1}H$ and $^{13}C$ spectra of 2k
$^1$H and $^{13}$C spectra of 21
$^1$H and $^{13}$C spectra of 2m
$^1$H and $^{13}$C spectra of 2n
$^1$H and $^{13}$C spectra of 2o
$^{1}H$ and $^{13}C$ spectra of 2p
$^1$H and $^{13}$C spectra of 2q
\(^1\text{H}\) and \(^{13}\text{C}\) spectra of 2r
$^1$H and $^{13}$C spectra of 2s
$^1$H and $^{13}$C spectra of 2t
$^1$H and $^{13}$C spectra of 2u
$^1$H and $^{13}$C spectra of 2v
$^1$H and $^{13}$C spectra of 2w
$^1$H and $^{13}$C spectra of 2x
\[ ^1H \text{ and } ^{13}C \text{ spectra of } 2y \]
$^1\text{H}$ and $^{13}\text{C}$ spectra of $2z$
\(^{1}\text{H}\) and \(^{13}\text{C}\) spectra of 2aa
$^1$H and $^{13}$C spectra of 4a
$^1$H and $^{13}$C spectra of 4b
$^1\text{H}$ and $^{13}\text{C}$ spectra of 4c
$^1$H and $^{13}$C spectra of 4d
$^{1}H$ and $^{13}C$ spectra of 4e
$^1$H and $^{13}$C spectra of 4f
$^1$H and $^{13}$C spectra of $4g$
$^1$H and $^{13}$C spectra of 4h
$^1$H and $^{13}$C spectra of 4i
$^1$H and $^{13}$C spectra of 4j
$^1$H and $^{13}$C spectra of 4k
$^{1} \text{H and }^{13} \text{C spectra of 4l}$
$^1\text{H}$ and $^{13}\text{C}$ spectra of 4m
\(^1\)H and \(^{13}\)C spectra of 9
$^{19}$F spectra of 9
$^1$H and $^{13}$C spectra of 13
$^1$H and $^{13}$C spectra of 14
$^1$H and $^{13}$C spectra of 16
$^1$H and $^{13}$C spectra of 17
$^{13}$H and $^{13}$C spectra of 18
$^1$H and $^{13}$C spectra of 19
$^1$H and $^{13}$C spectra of 20
$^1$H and $^{13}$C spectra of 24
\(^{1}\text{H}\) and \(^{13}\text{C}\) spectra of 27
$^{1}$H and $^{13}$C spectra of 29

S67
\(^1\)H and \(^{13}\)C spectra of 31