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Note

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# A Soluble Copper(I) Source and Stable Salts of Volatile Ligands for Copper-Catalyzed C-X Couplings

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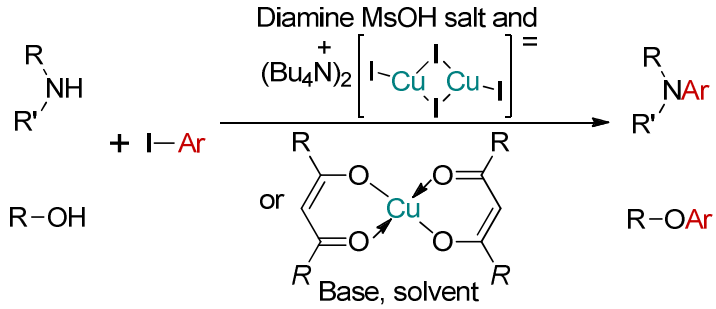



**Abstract**

A stable adduct of CuI with $Bu_4NI$, soluble in organic solvents has been identified as an effective catalyst for copper-catalyzed C-N and C-O couplings. In addition, stable non-hygroscopic salts of some high performance ligands (diamine MsOH salts/CuX and copper(II) diketonates) were shown to be of similar and sometimes greater reactivity to the literature reagents for these couplings. Furthermore, these more robust conditions result in more reproducible results.

The copper-catalyzed cross-coupling reactions of aryl halides with amine, alcohol and thiol nucleophiles have found widespread application in synthetic organic chemistry and industrial processes.[1 - 2] Despite their utility, anecdotal reports suggest these couplings can be notoriously unreliable, due in part to the insolubility of the copper source and base in the reaction medium. In addition, many of the high-performance ligands which have been developed for this class of reactions possess non-ideal physical and chemical properties such as volatility, hygroscopicity and in some cases air sensitivity. To address these issues, we report here the development of stable, non-volatile and non-hygroscopic salts of certain high-performance ligands and their use in Cu-catalyzed cross-coupling reactions.[3] In addition, we have identified a stable Cu(I) double salt which is readily soluble in most organic solvents and serves as a superior metal precursor for these reactions compared to traditional copper salts .

To address the issue of stability and ease of handling for some commonly used diamine ligands, a number of acids ($H_2SO_4$, MsOH, TfOH, $HBF_4$, $HPF_6$)[4] were screened that possessed conjugate bases with low coordinating potential. Of all the acids tested, methanesulfonic acid (MsOH) was found to give crystalline, air-stable, non-hygroscopic salts of diamines **1**-**4** (Scheme 1). To evaluate the performance of these salts as sources of the free ligand under cross-coupling conditions, all were tested against the model reaction involving the coupling of indole (**8**) with 4-iodoanisole (**9**).[5,6,7] The results shown in Table 1 using $Cs_2CO_3$ as base in three different solvents verify the MsOH salts of **1**-**4** perform as well as or better than the free diamine ligands in most cases.[8] The improvement was most evident for ligand **2**, which possesses the highest volatility of those tested. Furthermore, comparison

of free ligand **2** to **2**•2MsOH in triplicate experiments showed the standard deviation for yield variation using the MsOH salt was an order of magnitude less than using the free ligand **2**.[9]

**SCHEME 1. Ligands for Cu-catalyzed cross-coupling.**

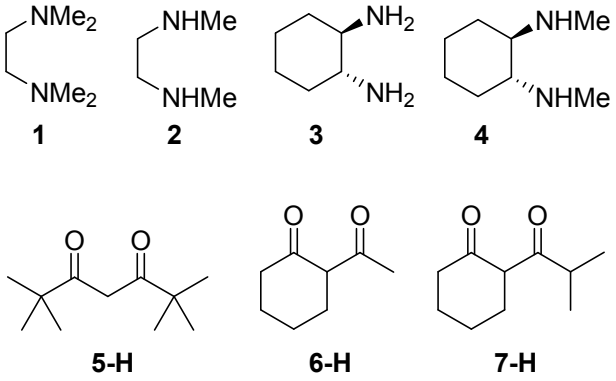
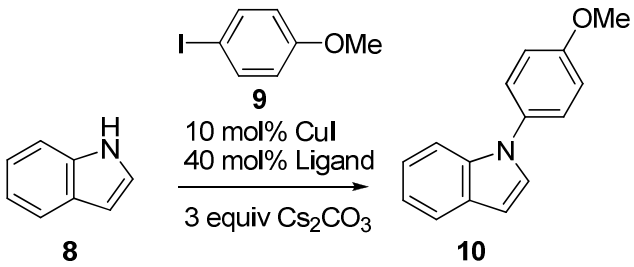



**TABLE 1. Evaluation of diamine MsOH salts in the N-arylation of indole.**[a]

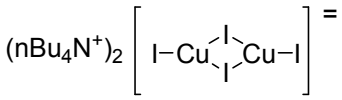



| | Solvent | Ligand | Yield | |
|---|---|---|---|---|
| | | | Free base | MsOH salt |
| 1 | toluene | **1** | 30 | 41 |
| 2 | CPME[b] | **1** | 49 | 56 |
| 3 | DMAc | **1** | 70 | 54 |
| 4 | toluene | **2** | 33 | 96 |
| 5 | CPME | **2** | 41 | 96 |
| 6 | DMAc | **2** | 57 | 78 |
| 7 | toluene | **3** | 96 | 96 |
| 8 | CPME | **3** | 93 | 93 |
| 9 | DMAc | **3** | 88 | 86 |
| 10 | toluene | **4** | 97 | 96 |
| 11 | CPME | **4** | 96 | 95 |
| 12 | DMAc | **4** | 66 | 87 |

[a] General reaction conditions: 1 μmol of CuI, 4 μmol of diamine ligand as either the free base or MsOH salt, 12 μmol of **8**, 10 μmol of **9**, 40 μmol of $Cs_2CO_3$ in 0.1 mL of solvent; 130 °C, 24h. Assay yields based on iodide **9** calculated from quantitative HPLC using internal standard. Virtually no (<2%) dehalogenation or homocoupling of iodide **9** was observed. [b] CPME = Cyclopentyl methyl ether

For the diketone ligands **5**-**7**, the potassium diketonate salts could be prepared and were found to be stable under nitrogen atmosphere, although they were not stable indefinitely in air. When these salts were tested as ligands in the *N*-arylation of indole with 4-iodoanisole, they performed more poorly than the corresponding free diketones (Table 2, Conditions A & B) Under the assmption that poor solubility of the potassium diketonates was contributing to their reduced reaction performance, the phase transfer catalyst *n*-$Bu_4NI$ was tested as an additive (Table 2, Condition C).[10] This combination gave yields across the various ligands and reaction solvents that matched, or in many cases exceeded, those obtained with the free ligands. This intriguing finding suggested *n*-$Bu_4NI$ might be affecting more than just the solubility of the ligand. Indeed, the poor solubility of CuI, the copper source of choice for most couplings, in most organic solvents can cause issues with catalyst activity and reproducibility. Copper(I) iodide forms a stable, isolable double salt with n$Bu_4NI$ (**11**);[11,12,13,14] however, its use in catalysis has not been explored until now.[15] We were able to prepare multigram quantities of **11** from CuI and *n*-$Bu_4NI$ in THF followed by addition of MTBE and crystallization. Complex **11** is a stable crystalline solid very soluble in THF and $CH_2Cl_2$, as well as the typical polar aprotic solvents. Using complex **11** as the copper source in the indole arylation test reaction with the potassium diketonate ligand salts (Table 2,

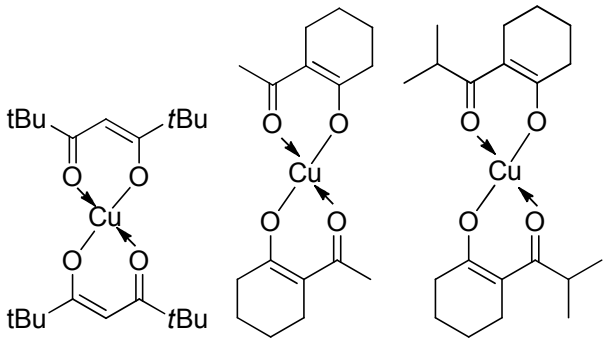
Condition D) not surprisingly gave results very similar to those seen using the admixture of CuI and *n*-$Bu_4NI$ (Table 2, Condition C). The use of the double salt was preferred, however, for issues of simplicity and ease of handling.



**11**

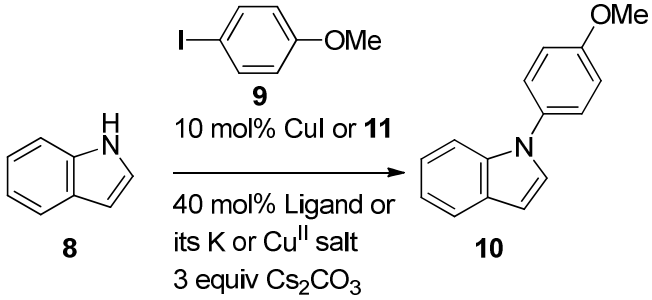
Although formation of the potassium diketonate salts afforded solid ligands with lower volatility and more desirable handling properties compared to the free ligands, the poor stability and solubility of these salts limited their ultimate utility, even though the latter effects could be mitigated by the addition of *n*-$Bu_4NI$ or the use of **11** as copper source. The ideal ligand salt would be an air and moisture stable solid, soluble in organic solvents and would incorporate the copper metal. Thus, copper(II) diketonates $\mathbf{5_2Cu}$, $\mathbf{6_2Cu}$ and $\mathbf{7_2Cu}$ (Scheme 2) were readily synthesized and found to be air stable solids which are readily soluble in organic solvents.[16] Furthermore, these complexes exhibited excellent catalytic activity in the model reaction shown in Table 2, in most cases matching the best activity seen with the other systems, and in the case of ligand **6** in CPME or DMAC giving clearly superior performance to the other systems (Table 2, Entries 5 and 6). For the coupling of **8** with **9** using as little as 1 mol% of **2•2MsOH/11** or $\mathbf{7_2Cu}$ gave ≥ 97% conversion to **10** with 3 equiv $Cs_2CO_3$ in toluene at 130 °C after 24h.

**SCHEME 2. Copper(II) diketonates.**




**$5_2$Cu** **$6_2$Cu** **$7_2$Cu**

**TABLE 2. Evaluation of diketonate salts in the N-arylation of indole.**[a]

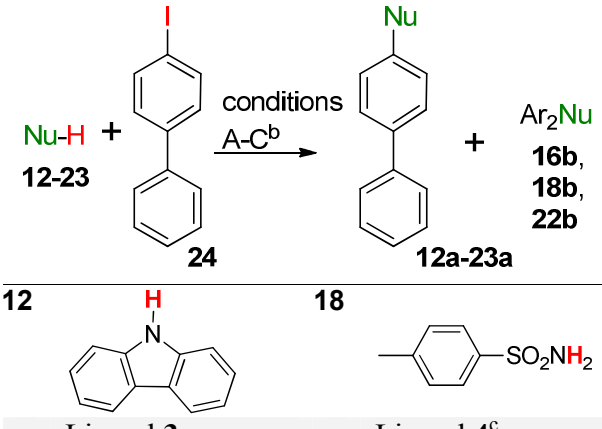



| | | | Conditions[b] | | | | |
|---|---|---|---|---|---|---|---|
| | Solvent | Ligand | A | B | C | D | E |
| 1 | toluene | **5** | 87 | 67 | 96 | 96 | 89 |
| 2 | CPME | **5** | 91 | 81 | 93 | 96 | 94 |
| 3 | DMAc | **5** | 95 | 84 | 89 | 95 | 90 |
| 4 | toluene | **6** | 54 | 18 | 88 | 80 | 85 |
| 5 | CPME | **6** | 72 | 48 | 78 | 76 | 91 |
| 6 | DMAc | **6** | 63 | 64 | 83 | 74 | 99 |
| 7 | toluene | **7** | 90 | 49 | 85 | 90 | 89 |
| 8 | CPME | **7** | 91 | 86 | 85 | 91 | 90 |
| 9 | DMAc | **7** | 75 | 72 | 90 | 92 | 96 |

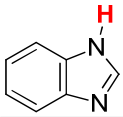
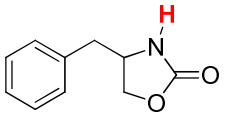
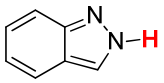
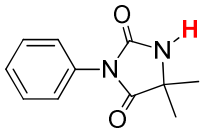
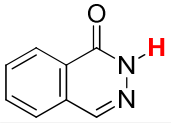
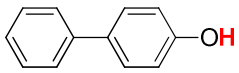
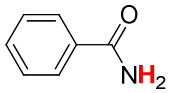
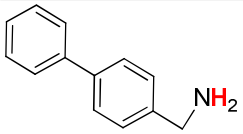
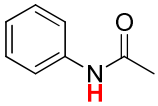
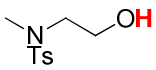
[a] General reaction conditions: see Table 1. [b] Conditions: A) 40 mol% free ligand, 10% CuI; B) 10% CuI, 40 mol% **Ligand**-K; C) 10% CuI, 40 mol% **Ligand**-K, 10 mol% $n$Bu$_4$NI; D) 40 mol% **Ligand**-K, 10 mol% **11**; E) 10 mol% **Ligand**$_2$-Cu. Assay yields based on iodide **9** calculated from quantitative HPLC using internal standard. Virtually no (<2%) dehalogenation or homocoupling of iodide **9** was observed in all reactions.

In order to show scope and utility for the new conditions, twelve substrates **12-23** bearing a variety of nitrogen and oxygen nucleophilic centers were coupled to 4-iodobiphenyl in dioxane using $Cs_2CO_3$ as base (Table 3), and the results compared to those obtained using the free ligands and CuI as copper source. Employing the MsOH salts of diamine ligands **2-4** in conjuction with **11** as copper source, good to excellent yields of products were obtained in the N-arylation of various amides and heterocycles (Table 3, Condition A). In many cases, the results with the ligand salt closely mirrored that obtained with the free ligand (e.g., **13**, **15**, **16** and **17**) or showed slight improvement (cf. **12**, **18**, **19**).[17,18,19,20,21,22] However, with indazole substrate **14** the traditional conditions almost completely failed to yield any coupled product, while the ligand salt with **11** gave excellent yields of coupled product. Likewise, the Cu(II) salt of diketone ligand **5** gave dramatically higher yields in the N-arylation of hydantoin **20** than those obtained with the free ligand system. Marked improvements in yield were also seen in the C-O couplings of phenol **21** and aliphatic alcohol **23** with *p*-iodobiphenyl catalyzed by Cu(II) salts of ligands **5** and **6**.[23,24,25]

**TABLE 3. Scope and utility of copper-catalyzed N- and O-arylation conditions.**[a]




| 12 | 18 |
|---|---|
|  |  |
| Ligand **3**<br>A: 88(85)%<br>B: 71% | Ligand **4**[c]<br>A: 63/10(62/6)%<br>B: 42/6% |

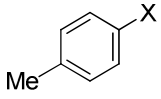
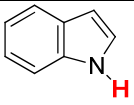
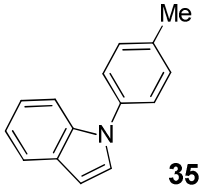
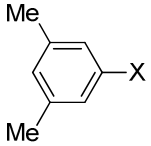
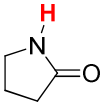
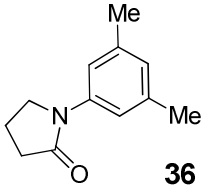
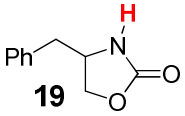
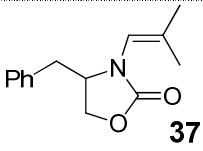
| | | | |
|---|---|---|---|
| **13** |  | **19** |  |
| | Ligand **3**<br>A: 97(93)%<br>B: 94% | | Ligand **2**<br>A: 96(90)%<br>B: 88% |
| **14** |  | **20** |  |
| | Ligand **3**<br>A: 94(89)%<br>B: 10% | | Ligand **5**<br>C: 97(90)%<br>B: 7% |
| **15** |  | **21** |  |
| | Ligand **3**<br>A: 90(80)%<br>B: 91% | | Ligand **5**<br>C: 88(85)%<br>B: 42% |
| **16** |  | **22** |  |
| | Ligand **4**[c]<br>A: 48/24(49/21)%<br>B: 48/18% | | Ligand **7**[c]<br>C: 72/22(66/23)%<br>B: 67/26% |
| **17** |  | **23** |  |
| | Ligand **4**<br>A: 84(82)%<br>B: 85% | | Ligand **7**<br>C: 86(83)%<br>B: 50% |

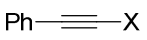
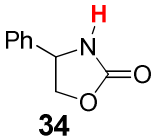
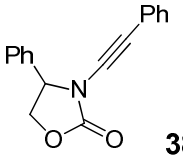
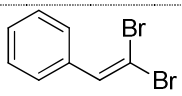
[a] Solution assay yields determined using quantitative HPLC. Isolated yields are given in parentheses. Yields based on the nucleophile **12**-**15**, **17**, **19**-**21**, **23**. In cases where mono and bis-arylation mixtures were obtained yields are based on iodide **24**. [b] General reaction conditions: 1.0 equiv. of Nu-H **12**-**23**, 1.2 equiv. of **24**, 4 equiv. of $Cs_2CO_3$, 0.1 M in 1,4-dioxane at 130 °C, 24h. Specific conditions: A) 10 mol% of **11**, 40 mol% of ligand MsOH salt; B) 10 mol% of CuI, 40 mol% of free ligand; C) 10 mol% of **Ligand**$_2$-Cu. Toluene and DMAc were explored as solvents as well (full details in Supporting Information) [c] Mixtures

of mono- and bis-arylated products were obtained; yields of mono-arylated/bis-arylated products based on iodide **24** are displayed.

Further scope was demonstrated for the electrophilic coupling partner using aryl, vinyl and alkynyl bromides and iodides (Table 4) using **11** as the copper source and the MsOH salt of the ligand. The results were similar to those obtained in the literature using free ligands with a conventional copper source such as CuI. Electron rich aryl bromides and iodides **25-28** gave good yields of coupled products.[18,22] Vinyl bromide **29** smoothly reacted with oxazolidinone **19** to provide enamine **37**.[17] Ynamine **38** was obtained from halophenylacetylenes **30** and **31**[26] as well as from 1,1-dibromoalkyne **32**.[27]

**TABLE 4. Scope and utility of copper-catalyzed C-N coupling conditions with various halides.**[a]

| Halide | Nucleophile | Product |
|---|---|---|
|  |  **8** |  **35** |
| **25**: X=Br | 96% condition A | |
| **26**: X=I | 96% condition A | |
|  |  **33** |  **36** |
| **27**: X=Br | 86% condition B | |
| **28**: X=I | 88% condition B | |
|  |  **19** |  **37** |

| | | | |
|---|---|---|---|
| **29** | 95% condition C |  |   |
| | | **34** | **38** |
| **30**: X=Br | 76% condition D | | |
| **31**: X=I | 82% condition D | | |
|  | | **34** | **38** |
| **32** | 80% condition E | | |

[a] In all reactions 1.2 equiv of halide was used. Condition A: 5 mol% **11**, 10 mol% **2•2MsOH**, 3 equiv $K_2CO_3$ in 1,4-dioxane, 110 °C, 24h. Condition B: 5 mol% **11**, 10 mol% **2•2MsOH**, 3 equiv $K_2CO_3$ in toluene, 100 °C, 24h. Condition C: 5 mol% **11**, 10 mol% **2•2MsOH**, 3 equiv $K_2CO_3$ in toluene, 90 °C, 24h. Condition D: 5 mol% **11**, 10 mol% **2•2MsOH**, 3 equiv $K_2CO_3$ in toluene, 110 °C, 24h. Condition E: 12 mol% **11**, 18 mol% **2•2MsOH**, 5 equiv $Cs_2CO_3$ in 1,4-dioxane, 60 °C, 24h. Isolated yields after chromatography are displayed.

In conclusion, we have demonstrated that stable, easily handled MsOH salts of volatile diamine ligands perform as well as the free diamines. We have also demonstrated the utility of copper(I) double salt **11** which performs as well as or better than CuI as copper source and gives more reproducible results. Finally, we have shown that copper(II) diketonates perform as well as or superior to the free diketones or their potassium salts. The stability and solubility of **11** and the copper(II) diketonates will make copper catalyzed couplings more reliable and robust reactions.

**Experimental section**

***N,N,N′,N′*-Tetraemethylethylenediamine bis(methanesulfonic acid) salt (1•2MsOH).** Methanesulfonic acid (40 mmol) in 1:1 (vol/vol) EtOAc-EtOH (10 mL) was added over 10 min to *N,N,N′,N′*-tetramethylethylenediamine (40 mmol) in 1:1 (vol/vol) EtOAc-EtOH (10 mL) in a 100 mL 3 neck round bottom flask equipped with a reflux condenser and magnetic stirrer. The temperature was allowed to reach reflux during the addition and EtOAc (30 mL) was added over 10 min at 60 °C. The resulting slurry was cooled to 5 °C over 30 min and filtered. The solid was washed with 4:1 (vol/vol) EtOAc-EtOH (20 mL) and EtOAc (20 mL) then dried under a stream of nitrogen to provide **1•2MsOH** (10.61 g, 86%). White crystalline solid: mp: 147-149 °C. $^{1}$H NMR (400MHz, $D_2O$) δ 3.68 (s, 4H), 3.03 (s, 12H), 2.85 (s, 6H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 51.1, 43.5, 38.5. Anal. Calcd. for $C_8H_{24}N_2O_6S_2$: C, 31.15; H, 7.84; N, 9.08; O, 31.13; S, 20.79. Found: C, 31.16; H, 7.67; N, 9.03.

***N,N′*-Dimethylethylenediamine bis(methanesulfonic acid) salt (2•2MsOH).** Methanesulfonic acid (60 mmol) in EtOH (5 mL) was added over 10 min to *N,N′*-dimethylethylenediamine (40 mmol) in EtOH (5 mL) in a 100 mL 3 neck round bottom flask equipped with a reflux condenser and magnetic stirrer. The temperature was allowed to reach reflux during the addition and EtOAc (30 mL) was added over 10 min at 60 °C. The resulting slurry was cooled to 5 °C over 30 min and filtered. The solid was washed with 9:1 (vol/vol) EtOAc-EtOH (20 mL) and EtOAc (20 mL) then dried under a stream of nitrogen to provide **2•2MsOH** (8.16 g, 73%). White crystalline solid: mp: 103-105 °C. $^{1}$H NMR (400MHz, $CD_3SOCD_3$) δ 8.64 (br s, 4H), 3.23 (s, 4H), 2.62 (s, 6H), 2.45 (s, 6H). $^{13}$C NMR (100MHz, $CD_3SOCD_3$) δ 43.9. 39.7, 32.9. Anal. Calcd. for $C_6H_{20}N_2O_6S_2$: C, 25.70; H, 7.19; N, 9.99; O, 34.24; S, 22.87. Found: C, 25.72; H, 7.33; N, 9.89.

***trans*-1,2-Cyclohexanediamine methanesulfonic acid salt (3•MsOH).** Methanesulfonic acid (25 mmol) in EtOAc (10 mL) was added over 10 min to *trans*-1,2-cyclohexanediamine (25 mmol) in EtOAc (20 mL) in a 100 mL 3 neck round bottom flask equipped with a reflux condenser and magnetic stirrer. The temperature was allowed to reach reflux during the addition. The resulting slurry was cooled to 5 °C over 30 min and filtered. The solid was washed with EtOAc (20 mL) then dried under a stream of nitrogen to provide **3•MsOH** (5.13 g, 98%). White crystalline solid: mp: 107-109 °C. $^{1}$H NMR (400MHz, $CD_3SOCD_3$) δ 5.28 (br s, 5H), 2.51 (m, 2H), 2.36 (s, 3H), 1.88 (m, 2H), 1.64 (m, 2H), 1.18 (m, 4H). $^{13}$C NMR (100MHz, $CD_3SOCD_3$) δ 54.3, 39.7, 32.3, 24.2. Anal. Calcd. for $C_7H_{18}N_2O_3S$: C, 39.98; H, 8.63; N, 13.32; O, 22.82; S, 15.25. Found: C, 39.64; H, 8.81; N, 13.06.

***trans*-*N,N′*-Dimethyl-1,2-Cyclohexanediamine bis(methanesulfonic acid) salt (4•2MsOH).** Methanesulfonic acid (40 mmol) in EtOAc (10 mL) was added over 10 min to *trans*-*N,N′*-dimethylethylenediamine (20 mmol) in EtOAc (20 mL) in a 100 mL 3 neck round bottom flask equipped with a reflux condenser and magnetic stirrer. The temperature was allowed to reach reflux during the addition. The resulting slurry was cooled to 5 °C over 30 min and filtered. The solid was washed with EtOAc (20 mL) then dried under a stream of nitrogen to provide **4•2MsOH** (6.61 g, 99%). White crystalline solid: mp: 151-153 °C. $^{1}$H NMR (500MHz, $CD_3SOCD_3$) δ 8.70 (br s, 4H), 3.40 (m, 2H), 2.65 (s, 6H), 2.45 (s, 6H), 2.06 (m, 2H), 1.64 (m, 2H), 1.57 (m, 2H), 1.30 (m, 2H). $^{13}$C NMR (125MHz, $CD_3SOCD_3$) δ 55.8, 30.4, 24.2, 21.1. Anal. Calcd. for $C_{10}H_{26}N_2O_6S_2$: C, 35.91; H, 7.84; N, 8.38; O, 28.70; S, 19.17. Found: C, 36.02; H, 8.10; N, 8.24.

**Bis(2-isobutyrylcyclohexanone) copper(II) complex ($7_2$Cu).** A 500mL round bottomed flask equipped with a magnetic stir bar was charged with $Cu(OAc)_2 \bullet H_2O$ (19.97g 0.10mol), methanol (200mL), and water (20mL). The mixture was heated to reflux to give a homogenous blue-green solution, and a solution of 2-isobutyrylcyclohexanone (33.65g, 0.20mol) in MeOH (20mL) was added over 30-60seconds to give a homogenous olive green solution. The mixture was cooled to 20 °C over 1h and water (200mL) was added over 1h. The solid was filtered off and was washed with 1:1 vol/vol methanol-water (200mL), then with ice cold methanol (50mL), then with ice cold *t*BuOMe (50mL) and finally with hexane (200mL). The solid was dried under a stream of nitrogen to provide the copper (II) diketonate salt (35.5g, 89%) as air stable fluffy solid. Olive green crystalline solid: mp: 200-201 °C. Anal. Calcd. for $C_{20}H_{30}CuO_4$: C, 60.36; H, 7.60; Cu, 15.97; O, 16.08. Found: C, 60.20; H, 7.53; Cu, 16.23; N, <0.05.

**Copper (I) iodide tetra *n*-butylammonium iodide dimeric complex ($n$Bu$_4$N$^+$)$_2$(Cu$_2$I$_4$)$^=$ (11).** A 3L 3-neck round bottomed flask equipped with mechanical stirrer was charged with CuI (209.48g, 1.10mol), $n$Bu$_4$NI (410.01g, 1.11mol) and peroxide free (inhibited with BHT) anhydrous deoxygenated THF (500mL) under nitrogen atmosphere. The mixture was warmed (48 °C) until a homogenous colorless to pale yellow solution was obtained. The mixture was cooled to 30 °C and several mg of crystalline ($n$Bu$_4$N$^+$)$_2$(Cu$_2$I$_4$)$^=$ was added. The mixture was cooled to 6 °C over 60 min and degassed *t*BuOMe (750mL) was added over 1h at 6°C. The mixture was stirred for 1h at 6 °C. The crystalline solid was filtered off and

washed with degassed 2:1 vol/vol *t*BuOMe-THF (450mL), then with 9:1 vol/vol *t*BuOMe-THF (450mL) and finally with *t*BuOMe (800mL). The solid was dried under a stream of nitrogen to provide $(n\mathrm{Bu_4N^+})_2(\mathrm{Cu_2I_4})^=$ (615.8g) in virtually quantitative yield as a white to pale tan granular crystalline solid (MW=559.82 as monomer); mp: 90-92 °C. $^1$H NMR (500MHz, $\mathrm{CDCl_3}$) δ 3.32 (m, 16H), 1.71 (m, 16H), 1.51 (apparent hextet, $J$ = 7.3 Hz, 16H), 1.05 (t, $J$ = 7.3 Hz, 24H). $^{13}$C NMR (125MHz, $\mathrm{CDCl_3}$) δ 59.6, 24.6, 20.1, 14.0. Anal. Calcd. for $\mathrm{C_{32}H_{72}Cu_2I_4N_2}$: C, 34.33; H, 6.48; Cu, 11.35; I, 45.34; N, 2.50. Found: C, 34.54; H, 6.63; Cu, 11.11; N, 2.43.

**Procedures for reactions conducted to determine isolated yields.** All reactions were performed under nitrogen with magnetic stirring. Reactions were performed in the cases of nucleophilic substrates **10** and **12**-**19** using 1.5 mmol nucleophile, 1.8 mmol **24**, 0.15 mmol **11**, 0.6mmol ligand salt (shown in Table 3) and 6 mmol $\mathrm{Cs_2CO_3}$ in 1,4-dioxane (2 mL), 130 °C, 24h; in case of nucleophilic substrates **20**-**23** using 1.5 mmol nucleophile, 1.5 mmol **24**, 0.15 mmol $\mathrm{ligand_2Cu}$ and 6mmol $\mathrm{Cs_2CO_3}$ in 1,4-dioxane (2 mL), 130 °C, 24h. Reactions were followed by workup with $\mathrm{CHCl_3}$/5% aq $\mathrm{Na_2EDTA}$ and crystallization by addition of heptane. Isolated yields are based on the nucleophile **12**-**15**, **17**, **19**-**21**, **23**. In cases where mono and bis-arylation mixtures were obtained from substrates **16**, **18**, and **22** isolated yields are based on iodide **24**; and are for monoarylated/bisarylated product mixtures that cocrystallized during isolation. Pure samples of monoarylated and bisarylated products were prepared by purification of the monoarylated/bisarylated mixtures by preparative TLC (silica, *t*BuOMe/hexane)

**1-(4-methoxyphenyl)-1H-indole (10).** 305mg, 91% yield. White crystalline solid: mp: 70-71 °C. $^{1}$H NMR (500MHz, $CDCl_3$) δ 7.72 (m, 1H), 7.49 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.43 (m, 2H), 7.31 (d, *J* = 3.2 Hz, 1H), 7.24 (m, 1H), 7.19 (m, 1H), 706 (m, 2H), 7.34 (d, *J* = 3.2 Hz, 1H), 3.90 (s, 3H). $^{13}$C NMR (125MHz, $CDCl_3$) δ 158.5, 136.6, 133.1, 129.2, 128.5, 126.2, 122.3, 121.2, 120.3, 114.9, 110.6, 103.1, 55.8. MS (ESI): 224 $[M + H]^+$. Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27; O, 7.17. Found: C, 80.49; H, 5.59; N, 6.10.

**9-([1,1'-biphenyl]-4-yl)-9H-carbazole (12a).** 407mg, 85% yield. White crystalline solid: mp: 223-224 °C. $^{1}$H NMR (400MHz, $CDCl_3$) δ 8.20 (ddd, *J* = 7.7, 0.8, 0.8 Hz, 2H), 7.85 (ddd, *J* = 8.6, 2.3, 2.3 Hz, 2H), 7.72 (ddd, *J* = 7.4, 1.7, 1.7 Hz, 2H), 7.67 (ddd, *J* = 8.9,2.2, 2.2 Hz, 2H), 7.56-7.42 (m, 7H), 7.34 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 2H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 141.1, $140.5_3$, $140.5_0$, 137.1, 129.2, 128.7, 127.9, 127.6, 127.6, 127.4, 126.2, 123.7, 120.5, 120.2. MS (ESI): 320 $[M + H]^+$. Anal. Calcd. for $C_{24}H_{17}N$: C, 90.25; H, 5.36; N, 4.39. Found: C, 90.01; H, 5.01; N, 4.16.

**1-([1,1'-biphenyl]-4-yl)-1H-benzo[d]imidazole (13a).** 377mg, 93% yield. White crystalline solid: mp: 173-174 °C. $^{1}$H NMR (500MHz, $CDCl_3$) δ 8.17 (m, 1H), 7.92 (m, 1H), 7.80 (dt, *J* = 9.1, 2.3 Hz, 2H), 7.66 (m, 2H), 7.61 (om, 3H), 7.51 (m, 2H), 7.43 (m, 1H), 7.37 (om, 2H). $^{13}$C NMR (125MHz, $CDCl_3$) δ 144.4, 142.4, 141.3, 140.0, 135.7, 133.9, 129.2, 128.9, 128.1, 127.3, 124.5, 123.9, 123.0, 120.9, 110.7. MS (ESI): 271 $[M + H]^+$. Anal. Calcd. for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.12; H, 4.97; N, 10.04.

**1-([1,1'-biphenyl]-4-yl)-1H-indazole (14a).** 361mg, 89% yield. White crystalline solid: mp: 169-170 °C. $^{1}$H NMR (500MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.83 (om, 4H), 7.79 (m, 2H), 7.68 (m, 2H), 7.59 (m, 3H), 7.40 (m, 1H), 7.27 (m, 1H). $^{13}$C NMR (125MHz, $CDCl_3$) δ 140.4, 139.7, 139.6, 139.0, 135.7, 129.1, 128.2, 127.7, 127.4, 127.3, 125.6, 123.1, 121.8, 121.6, 110.7. MS (ESI): 271. HRMS (ESI) found *m/z* 271.1222 $[M + H]^+$, calcd for $C_{19}H_{14}N_2$ + H 271.1230.

**2-([1,1'-biphenyl]-4-yl)phthalazin-1(2H)-one (15a).** 358mg, 80% yield. White crystalline solid: mp: 187-189 °C. $^{1}$H NMR (400MHz, $CDCl_3$) δ 8.55 (m, 1H), 8.33 (s, 1H), 7.85 (om, 2H), 7.80-7.76 (om, 3H), 7.72 (m, 2H), 7.65 (m, 2H), 7.48 (m, 2H), 7.39 (m, 1H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 159.4, 141.3, 140.8, 140.7, 138.8, 133.7, 132.2, 129.7, 129.0, 128.8, 127.7, 127.5, 127.4, 126.3, 126.1. MS (ESI): 299. HRMS (ESI) found *m/z* 299.1170 $[M + H]^+$, calcd for $C_{20}H_{14}N_2O$ + H 299.1179.

Cocrystallized mixture of **16a** and **16b**: 402mg, 70% yield.

***N*-([1,1'-biphenyl]-4-yl)benzamide (16a).** White crystalline solid: mp: 233-234 °C. $^{1}$H NMR (400MHz, $CD_3SOCD_3$) δ 10.35 (s, 1H), 7.98 (m, 2H), 7.91 (m, 2H), 7.69 (m, 4H), 7.61 (m, 1H), 7.56 (m, 2H), 7.46 (m, 2H), 7.34 (m, 1H). $^{13}$C NMR (100MHz, $CD_3SOCD_3$) δ 165.5, 139.7, 138,7, 135.2, 134.9, 131.6, 128..9, 128.4, 127.6, 127.0, 126.8, 126.3, 120.6. MS (ESI): 274 $[M + H]^+$. Anal. Calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12; O, 5.85. Found: C, 83.37; H, 5.45; N, 5.09.

***N*,*N*-di([1,1'-biphenyl]-4-yl)benzamide (16b).** White crystalline solid: mp: 208-209 °C. $^{1}$H NMR (400MHz, $CD_3SOCD_3$) δ 7.65 (m, 8H), 7.51 (m, 2H), 7.45 (m, 4H), 7.37-7.27 (m, 9H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 170.9, 143.3, 140.3, 139.4, 136.3, 130.5, 129.5, 129.0, 128.2, 128.0, 127.9, 127.7, 127.2. MS (ESI): 426 $[M + H]^+$.

***N*-([1,1'-biphenyl]-4-yl)-*N*-phenylacetamide (17a).** 853mg, 82%. White crystalline solid: mp: 106-107 °C. $^{1}$H NMR (400MHz, $CDCl_3$, 25 °C) δ 7.59 (m, 4H), 7.47-7.32 (om, 10H), 2.12 (s, 3H). $^{1}$H NMR (600MHz, $CD_3SOCD_3$, 77 °C) δ 7.64 (m, 4H), 7.47-7.29 (om, 10H), 1.99 (s, 3H). $^{13}$C NMR (150MHz, $CD_3SOCD_3$, 77 °C) δ 169.7, 143.8, 143.1, 139.9, 139.1 (br), 129.7, 129.3, 128.3 (br), 127.9, 127.8, 127.4 (br), 127.1, 23.8. MS (ESI): 288 $[M + H]^+$.

Cocrystallized mixture of **18a** and **18b**: 412mg, 68% yield.

***N*-([1,1'-biphenyl]-4-yl)-4-methylbenzenesulfonamide (18a).** White crystalline solid: mp: 157-158 °C. $^{1}$H NMR (400MHz, $CD_3SOCD_3$) δ 10.35 (s, 1H), 7.70 (m, 2H), 7.55 (m, 4H), 7.42-7.28 (m, 5H), 7.19 (m, 2H), 3.34 (s, 3H). $^{13}$C NMR (125MHz, $CD_3SOCD_3$) δ 143.3, 139.3, 137.2, 136.8, 135.5, 129.7, 128.9, 127.3, 127.2, 126.7, 126.2, 120.1, 20.9. MS (ESI): 324 $[M + H]^+$. Anal. Calcd. for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33; O, 9.89; S, 9.91. Found: C, 70.46; H, 5.30; N, 4.36.

***N*,*N*-di([1,1'-biphenyl]-4-yl)-4-methylbenzenesulfonamide (18b).** White crystalline solid: mp: 182-183 °C. $^{1}$H NMR (500MHz, $CDCl_3$) δ 7.69 (dt, $J$ = 8.3, 1.8 Hz, 2H), 7.57 (om, 8H), 7.45 (m, 4H), 7.38 (om, 6H), (d, $J$ = 8.1 Hz, 2H), 2.47 (s, 3H). $^{13}$C NMR (125MHz, $CDCl_3$) δ

143.9, 140.9, 140.5, 140.3, 137.8, 129.8, 129.0 128.6, 128.2, 128.1, 127.8, 127.3, 21.8. MS (ESI): 476 $[M + H]^+$. Anal. Calcd. for $C_{31}H_{25}NO_2S$: C, 78.29; H, 5.30; N, 2.95; O, 6.73; S, 6.74. Found: C, 77.99; H, 5.19; N, 2.94.

**3-([1,1'-biphenyl]-4-yl)-4-benzyloxazolidin-2-one (19a).** 445mg, 90%. White crystalline solid: mp: 151-152 °C. $^1$H NMR (500MHz, $CDCl_3$) δ 7.69-7.61 (om, 6H), 7.47 (m, 2H), 7.38 (m, 1H), 7.34 (m, 2H), 7.30 (m, 1H), 7.17 (m, 2H), 4.71 (dddd, *J* = 9.4, 8.8, 4.8, 3.5 Hz, 1H), 4.39 (t, *J* = 8.5 Hz, 1H), 4.25 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.21 (dd, *J* = 13.8, 3.5 Hz, 1H), 2.83 (dd, *J* = 13.8, 9.4 Hz, 1H). $^{13}$C NMR (125MHz, $CDCl_3$) δ 155.7, 140.4, 138.3, 136.1, 135.4, 129.4, 129.2, 129.1, 128.2, 127.6, 127.5, 127.2, 122.0, 66.3, 57.5, 38.0. MS (ESI): 330 $[M + H]^+$. Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25; O, 9.71. Found: C, 80.24; H, 5.64; N, 4.20.

**1-([1,1'-biphenyl]-4-yl)-5,5-dimethyl-3-phenylimidazolidine-2,4-dione (20a).** 481mg, 90%. White crystalline solid: mp: 128-129 °C. $^1$H NMR (500MHz, $CDCl_3$) δ 7.69 (ddd, *J* = 8.6, 2.2, 2.2 Hz, 2H), 7.62 (m, 2H), 7.55-7.47 (om, 6H), 7.43-7.38 (om, 4H), 1.62 (s, 6H). $^{13}$C NMR (125MHz, $CDCl_3$) δ 175.4, 154.2, 141.7, 140.3, 133.4, 132.1, 129.3, 129.2, 129.1, 128.5, 128.3, 128.0, 127.4, 126.3, 63.7, 24.4. MS (ESI): 357 $[M + H]^+$. Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86; O, 8.98. Found: C, 77.14; H, 5.55; N, 7.74.

**4,4''-oxydi-1,1'-biphenyl (21a).** 411mg, 85%. White crystalline solid: mp: 198-199 °C. $^1$H NMR (500MHz, $CDCl_3$) δ 7.59 (m, 8H), 7.45 (m, 4H), 7.35 (m, 2H), 7.14 (m, 4H). $^{13}$C NMR

(125MHz, $CDCl_3$) δ 157.0, 140.8, 136.7, 129.0, 128.7, 127.3, 127.1, 119.4. Anal Calcd. for $C_{24}H_{18}O$: C, 89.41; H, 5.63; O, 4.96. Found: C, 89.38; H, 5.59; N, <0.05.

Cocrystallized mixture of **22a** and **22b**: 583mg, 89% yield.

***N*-([1,1'-biphenyl]-4-ylmethyl)-[1,1'-biphenyl]-4-amine (22a).** White crystalline solid: mp: 180-182 °C. $^1$H NMR (500MHz, $CD_3SOCD_3$) δ 7.64 (m, 4H), 7.52 (m, 2H), 7.45 (om, 4H), 7.40-7.33 (om, 5H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.69 (m, 2H), 6.48 (t, *J* = 6.1 Hz, 1H), 4.36 (d, *J* = 6.1 Hz, 2H). $^{13}$C NMR (100MHz, $CD_3SOCD_3$) δ 148.2, 140.5, 140.0, 139.5, 138.6, 128.9, 128.7, 127.7, 127.5, 127.2, 127.1, 126.6, 126.5, 125.7, 125.4, 112.7, 46.0. MS (ESI): 336 $[M + H]^+$. Anal. Calcd. for $C_{25}H_{21}N$: C, 89.51; H, 6.31; N, 4.18. Found: C, 89.88; H, 5.97; N, 3.90.

***N*-([1,1'-biphenyl]-4-yl)-*N*-([1,1'-biphenyl]-4-ylmethyl)-[1,1'-biphenyl]-4-amine (22b).** White crystalline solid: mp: 197-198 °C. $^1$H NMR (500MHz, $CDCl_3$) δ 7.60 (m, 8H), 7.55 (m, 4H), 7.49-7.42 (om, 8H), 7.37-7.31 (om, 3H), 7.25 (m, 4H), 5.15 (s, 2H). $^{13}$C NMR (125MHz, $CDCl_3$) δ 147.4, 141.1, 140.9, 140.1, 138.3, 134.5, 129.0, 128.9, 128.1, 127.6, 127.4, 127.3, 127.2, 126.9, 126.8, 121.1, 56.3. MS (ESI): 488. HRMS (ESI) found *m/z* 488.2381 $[M + H]^+$, calcd for $C_{37}H_{29}N$ + H 488.2378.

***N*-(2-([1,1'-Biphenyl]-4-yloxy)ethyl)-*N*,4-dimethylbenzenesulfonamide (23a).** 475mg, 83% yield. White crystalline solid: mp: 154-155 °C. $^1$H NMR (400MHz, $CDCl_3$) δ 7.73 (ddd, *J* = 8.3, 1.9, 1.9 Hz, 2H), 7.57-7.50 (om, 4H), 7.43 (m, 2H), 7.32 (m, 3H), 6.93 (ddd, *J* = 8.9,

2.6, 2.6 Hz, 2H), 4.20 (t, *J* = 5.7 Hz, 2H), 3.48 (t, *J* = 5.7 Hz, 2H), 2.95 (s, 3H), 2.44 (s, 3H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 158.0, 143.7, 140.9, 135.2, 134.5, 130.0, 128.9, 128.4, 127.6, 127.0, 126.9, 115.0, 67.3, 49.6, 36.8, 21.7. MS (ESI): 382 $[M + H]^+$. Anal. Calcd. for $C_{22}H_{23}NO_3S$: C, 69.26; H, 6.08; N, 3.67; O, 12.58; S, 8.41. Found: C, 68.89; H, 5.70; N, 3.58.

**1-(*p*-Tolyl)-1H-indole (25).**

From bromide **25**: A mixture of **8** (140 mg, 1.2 mmol), bromide **25** (171 mg, 1 mmol), **11** (28 mg, 0.05mmol), **2•2MsOH** (29 mg, 0.1 mmol), $K_2CO_3$ (415 mg, 3 mmol) and 1,4-dioxane (3 mL) was heated to 110 °C with magnetic stirring for 24h. The mixture was cooled, filtered and chromatographed on silica gel using EtOAc/heptane to provide **35** (96%). White crystalline solid: mp: 38-39 °C. $^1$H NMR (500MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.47 (m, 2H), 7.39 (om, 3H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 2.6 Hz, 1H), 2.52 (s, 3H). $^{13}$C NMR (125MHz, $CDCl_3$) δ 137.5, 136.5, 136.2, 130.3, 129.4, 128.3, 124.5, 122.4, 121.3, 120.4, 110.7, 103.4, 21.2. MS (ESI): 208 $[M + H]^+$.

From iodide **26**: Same procedure as above except bromide **25** was replaced with iodide **26** (218 mg, 1mmol). (200 mg, 96%).

**1-(3,5-Dimethylphenyl)pyrrolidin-2-one (36).**

From bromide **27**: A mixture of **33** (102 mg, 1.2 mmol), bromide **27** (185 mg, 1 mmol), **11** (28 mg, 0.05mmol), **2•2MsOH** (29 mg, 0.1 mmol), $K_2CO_3$ (415 mg, 3 mmol) and toluene (3 mL) was heated to 100 °C with magnetic stirring for 24h. The mixture was cooled, filtered

and chromatographed on silica gel using EtOAc/heptane to provide **36** (86%). White crystalline solid: mp: 96-98 °C. $^{1}$H NMR (400MHz, $CDCl_3$) δ 7.22 (2, 1H), 6.82 (s, 1H), 3.84 (m, 2H), 2.59 (m, 2H), 2.33 (s, 6H). 2.14 (m, 2H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 174.3, 139.5, 138.6, 126.6, 119 1, 49.3, 33.0, 21.7, 18.3. MS (ESI): 190 $[M + H]^+$.

From iodide **28**: Same procedure as above except bromide **27** was replaced with iodide **28** (232 mg, 1 mmol). (182 mg, 88%).

**4-Benzyl-3-(2-methylprop-1-en-1-yl)oxazolidin-2-one (37).** A mixture of **19** (213 mg, 1.2 mmol), bromide **29** (135 mg, 1 mmol), **11** (28 mg, 0.05mmol), **2•2MsOH** (29 mg, 0.1 mmol), $K_2CO_3$ (415 mg, 3 mmol) and toluene (3 mL) was heated to 90 °C with magnetic stirring for 24h. The mixture was cooled, filtered and chromatographed on silica gel using EtOAc/heptane to provide **35** (95%). White crystalline solid: mp: 58-60 °C. $^{1}$H NMR (400MHz, $CDCl_3$) δ 7.36-7.23 (m, 3H), 7.16 (m, 2H), 5.70 (apparent heptet, $J$ = 1.4 Hz, 1H), 4.25 (m, 1H), 4.13 (om, 2H), 3.10 (dd, $J$ = 13.6, 3.8 Hz, 1H), 2.68 (dd, $J$ = 13.6, 9.1 Hz, 1H), 1.81 (d, $J$ = 1.2 Hz, 3H), 1.76 (d, $J$ = 1.2 Hz, 3H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 156.7, 135.8, 134.2, 129.3, 129.0, 127.3, 117.2, 66.9, 58.8, 38.8, 22.8, 18.5. MS (ESI): 232 $[M + H]^+$.

**4-Phenyl-3-(phenylethynyl)oxazolidin-2-one (38).**

From bromide **30**: A mixture of **34** (196 mg, 1.2 mmol), bromide **30** (181 mg, 1 mmol), **11** (28 mg, 0.05mmol), **2•2MsOH** (29 mg, 0.1 mmol), $K_2CO_3$ (415 mg, 3 mmol) and toluene (3 mL) was heated to 110 °C with magnetic stirring for 24h. The mixture was cooled, filtered and chromatographed on silica gel using EtOAc/heptane to provide **35** (200 mg, 76%). White

crystalline solid: mp: 132-134 °C. $^{1}$H NMR (400MHz, $CDCl_3$) δ 7.51-7.42 (om, 5H), 7.27 (m, 5H), 5.17 (dd, *J* = 8.6, 7.2 Hz, 1H), 4.82 (t, *J* = 8.9 Hz, 1H), 4.35 (dd, *J* = 8.9, 7.2 Hz, 1H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 155.7, 136.3, 131.7, 129.8, 129.6, 128.4, 128.3, 127.1, 122.3, 78.2,73.1, 71.0, 62.5. MS (ESI): 264 $[M + H]^+$.

From iodide **31**: Same procedure as above except bromide **30** was replaced with iodide **31** (228 mg, 1mmol); (216 mg, 82%).

From dibromoolefin **32**: A mixture of **34** (196 mg, 1.2 mmol), dibromoolefin **32** (262 mg, 1 mmol), **11** (67 mg, 0.12mmol), **2•2MsOH** (52 mg, 0.18 mmol), $Cs_2CO_3$ (1.63g, 5 mmol) and 1,4-dioxane (3 mL) was heated to 60 °C with magnetic stirring for 24h. The mixture was cooled, filtered and chromatographed on silica gel using EtOAc/heptane to provide **35** (200 mg, 76%).

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**Supporting Information.** General experimental methods, detailed tables of results and copies of $^{1}$H and $^{13}$C NMR spectra for compounds **10**, **12a**-**23a**, **16b**, **18b** and **22b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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