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# A REVIEW ON MICROWAVE ASSISTED COUPLING REACTIONS

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## ABSTRACT
For several years, there has been increasing interest in developing new cross-coupling reactions using different methods. The objective of this study was to review cross-coupling reactions, particularly the use of different solvents and microwave irradiation conditions. In conclusion, these methods may be useful for future decisions regarding the development of new compounds under assisted microwave irradiation.

**KEYWORDS**. Coupling reactions, irradiation, microwave.

## INTRODUCTION
In the literature there are several studies that show cross-coupling reactions furnishing carbon-carbon (C–C) and carbon–heteroatom (C-X) bonds, which has been increasing in the organic chemistry field.[i-iv] For example, a study showed the synthesis of compound 1-methyl-4-phenyl-quinolin-2-one (2) through a palladium-catalyzed Suzuki cross-coupling reaction from 4-Chloro-1-methyl-1H-quinolin-2-one (1) and phenylboronic acid using microwave irradiation (Figure 1).[v]

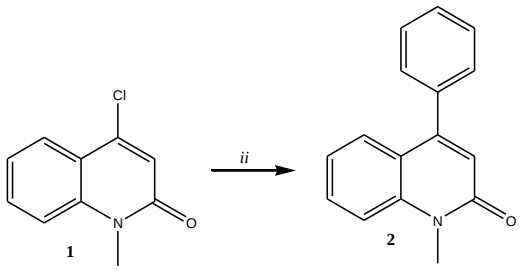



Figure 1. Synthesis of a 4-arylquinolin-2-one derivative (**2**). *Conditions and Reagents*: *i* = $PhB(OH)_2$, $Pd(OAc)_2$, $PPh_3$, dimethylformamide/water, MW (150 $^oC$), 30 min.

Other data displayed the preparation of biphenyl derivatives through the Suzuki cross-coupling reaction using Pd/graphene as a catalyst under microwave irradiation conditions (Figure 2 and Table 1).[vi]

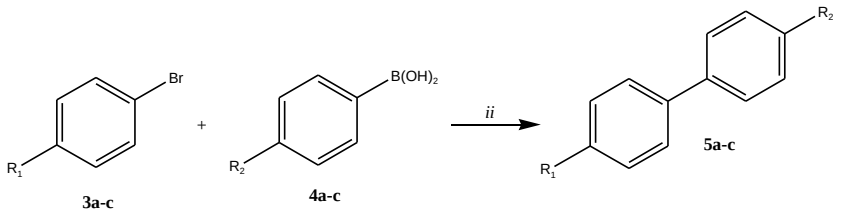
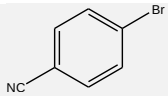
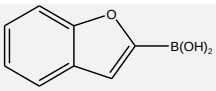
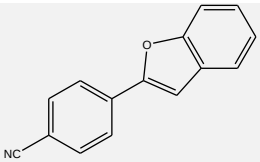
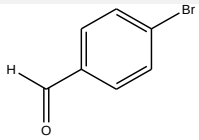
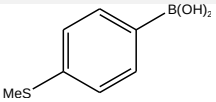
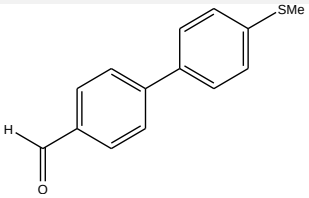
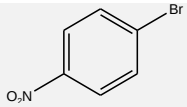
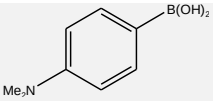
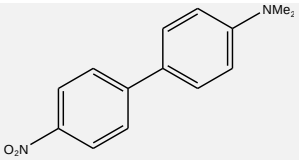



Figure 2. Synthesis of biphenyl derivatives (**5a-c**). *Conditions and Reagents*: *ii* = $K_2CO_3$, Pd/graphene, $H_2O$/EtOH (1:1), MW (80 $^oC$), 10 min.

Table 1. Synthesis of Biphenyl from aryl halides and boronic acids.

| Aril halide | Boronic acid | Product | Yield (%) |
|---|---|---|---|
|  3a |  4a |  5a | 90 |
|  3b |  4b |  5b | 92 |
|  3c |  4c |  5c | 85 |

Besides, a study shows the cross-coupling reaction of aryl sulfinates with nitriles in the presence of $Pd(O_2CCF_3)_2$, 6-methyl-2,2′-bipyridyl, and trifluoroacetic acid under microwave irradiation to form the compound 1-Phenyl-ethanone (Figure 3)[vii]

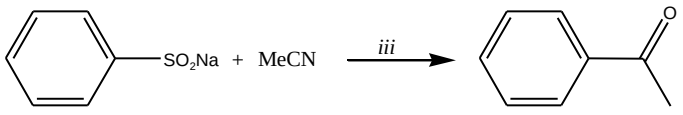



Figure 3. Synthesis of a 4-arylquinolin-2-one derivative (**2**). *Conditions and Reagents*: *iii* = $Pd(O_2CCF_3)_2$ and 6-methyl-2,2′-bipyridyl, trifluoroacetic acid, $H_2O$/THF (1:1), MW (100 $^OC$), 1 h.

Another report shows the preparation of the compound 2-[2-[[tert-butyl(dimethyl)silyl]oxymethyl]-4,5-dimethoxy-phenyl]benzaldehyde from (2-bromo-4,5-dimethoxy-phenyl)methoxy-tert-butyl-dimethyl-silane via a Suzuki-Miyaura reaction in the presence of (2-formylphenyl)boronic acid under microwave irradiation (Figure4).[viii]

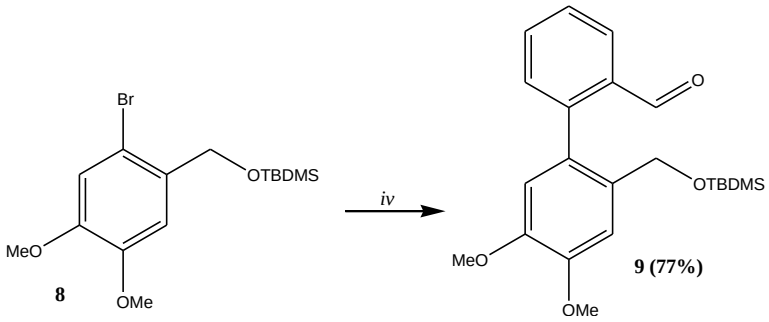



Figure 4. Synthesis of a biaryl-aldheyde analog (**8**). *Conditions and Reagents*: *iv* = (2-formylphenyl)boronic acid, $Pd(Ph_3P)_4$, $Cs_2CO_3$, dioxane/EtOH (2:1), MW (130 $^{O}$C), 15 min.

Buszek and Brown (2007) displayed the coupling of (E)-1-(3-oxobut-1-enyl)pyridinium tetrafluoroborate (**10**) with p-methoxyphenylboronic acid (**11**) to form the compound (*E*)-4-(4-methoxyphenyl)but-3-en-2-one (**12**) using tricyclohexylphosphine (PCy3) as a catalyst under microwave conditions (Figure 5).[ix]

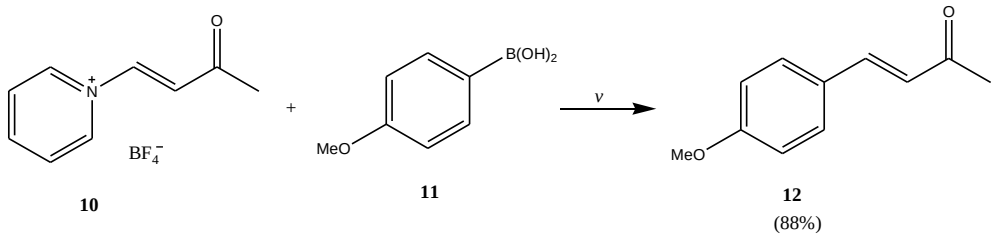
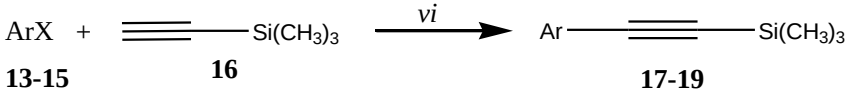



Figure 5. Synthesis of an enone derivative (**12**). *Conditions and Reagents*: *iv* = $Pd_2(dba)_3$, $PCy_3$, THF, MW (150 $^{o}$C), 12 min.

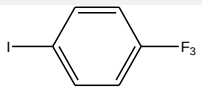
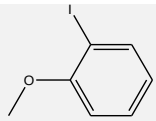
A study showed the Sonogashira Coupling reaction on Aryl Halides with Trimethylsilylacetylene using $Pd(PPh_3)_2Cl$ (Bis (triphenylphosphine)palladium chloride) as a catalyst under microwave assistance (Figure 6 and Table 2) to form some ethynyl-silane derivatives (**17-19**).[x]

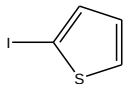



**13-15** **16** **17-19**

Figure 6. Synthesis of ethynyl-silane derivatives (**17-19**). *Conditions and Reagents*: *vi* = $Pd(PPh_3)_2Cl$, CuI, $Et_2NH$, DMF, MW (120 $^{o}$C).

Table 2. Aryl analogs involved in the synthesis of ethynyl-silane derivatives (17-19)

| Ar-X | Reaction time (min) | Yield (%) |
|---|---|---|
| | 5 | 97 |
|  13 | | |
|  14 | 5 | 99 |



5 86

15

Other data indicates the coupling of 1-tert-butyl-4-iodo-benzene (**20**) with 1-ethynyl-2-fluoro-benzene (**21**) in the presence of $Cs_2CO_3$ and N-methylpyrrolidinone to form the compound 1-tert-butyl-4-[2-(2-fluorophenyl)ethynyl]benzene (**22**) through a copper-catalyzed Sonogashira reaction under microwave irradiation (Figure 7).[xi]

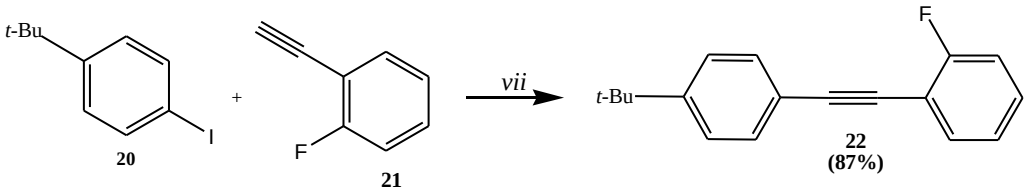



Figure 7. Synthesis of 1-*tert*-butyl-4-[2-(2-fluorophenyl)ethynyl]benzene (**22**). *Conditions and Reagents*: *vii* = CuI, $Cs_2CO_3$, N-methylpyrrolidinone, MW (195 $^oC$), 2-6 h.

Lipshutz and coworkers (2006), showed the preparation of 3,4-dimethoxy-6-methyl-2-(p-tolyl)benzaldehyde (**25**) from (2-formyl-5,6-dimethoxy-3-methyl-phenyl)4-methylbenzenesulfonate (**23**) and chloro(*p*-tolyl)zinc (**24**) in the presence of Ni/C (Figure 8).[xii]

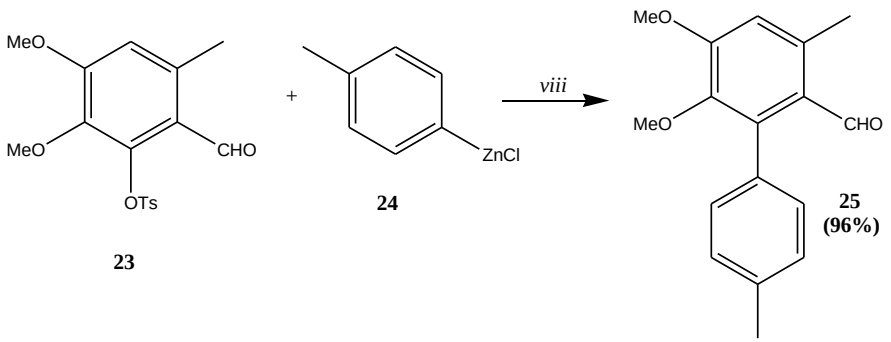



Figure 8. Synthesis of a biaryl derivative (**25**). *Conditions and Reagents*: *viii* = Ni/C (8%), $Ph_3P$, dioxane, MW (150 $^oC$), 15 min.

Other data displayed the synthesis of a bipyridine derivative (**28**) through the Negishi coupling reaction. In this way, the compound 2-Iodo-pyridine (**26**) reacted with bromo(2-pyridyl)zinc (**27**) in the presence of the $Ni/Al_2O_3$-$SiO_2$ system to form **28** (Figure9).[xiii]

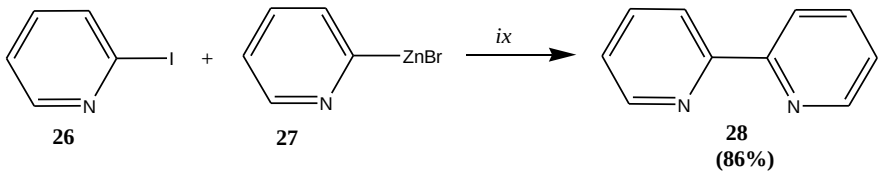



Figure 9. Synthesis of a biperidine derivative (**28**). *Conditions and Reagents*: *ix* = THF, $Ni/Al_2O_3$-$SiO_2$, $PPh_3$, MW (300 W), 1h.

Besides, the Stille cross-coupling reaction was carried out to synthesize1-methoxy-4-phenyl-benzene (**31**) from 4-iodoanisole (**29**) and tributyl(phenyl)stannane (**30**) using a dimeric ortho-palladate complex of tribenzylamine in different solvents and bases under assisted-microwave irradiation (Figure 10).[xiv]

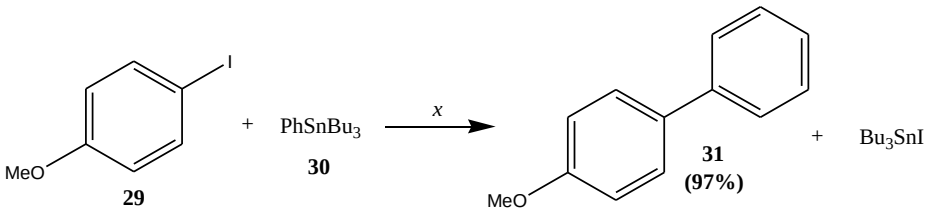



Figure 10. Synthesis of -methoxy-4-phenyl-benzene (**31**). *Conditions and Reagents*: *x* = palladacycle catalyst, $K_2CO_3$, DMF MW (100 $^oC$)

Other studies show the Buchwald-Hartwig double amination reaction.[xv] In this way, the compound 10H-phenoxazine (**32**) reacted with 1,4-dibromobenzene (**33**) to form the compound 10-(4-phenoxazin-10-ylphenyl)phenoxazine (**34**) using $Pd_2(dba)_3$ as a catalyst under microwave-assisted irradiation (Figure 11).

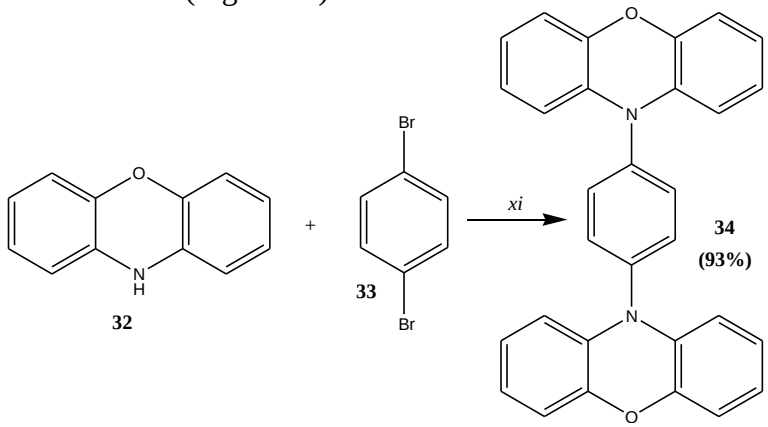



Figure 11. Synthesis of 10-(4-phenoxazin-10-ylphenyl)phenoxazine (**34**). *Conditions and Reagents*: *xi* = $Pd_2(dba)_3$, XPhos, *t*-BuONa, Toluene, MW (200W), 150 $^oC$, 30 min.

In addition, a report displays the palladium-catalyzed intramolecular Buchwald-Hartwig reaction using 2,6-diisopropyl aniline (**35**) and 1-bromo-2,4,6-triisopropyl benzene (**36**) as reagents to form the compound 2,6-diisopropyl-N-phenyl-aniline (**37**) in the presence of N,N-bis(diphenylphosphanyl)aniline or N,N-bis(diphenylphosphanyl)-2,6-diisopropyl-aniline (Figure 12).[xvi]

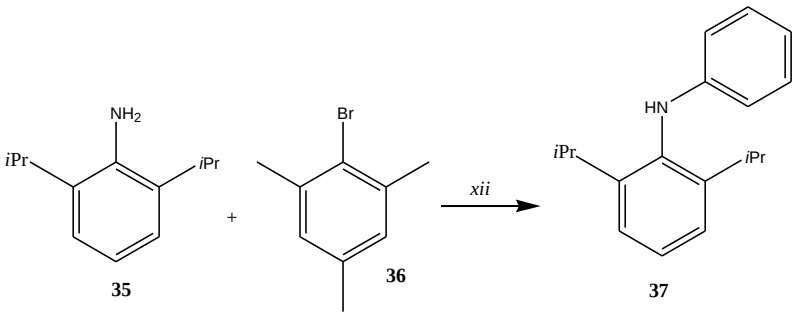



Figure 12. Synthesis of 2,6-diisopropyl-*N*-phenyl-aniline (3**7**). *Conditions and Reagents*: *xii* = *N*,*N*-bis(diphenylphosphanyl)aniline or *N*,*N*-bis(diphenylphosphanyl)-2,6-diisopropyl-aniline, NaO*t*Bu, Pd (dba)2, toluene, MW, 15 min.

On the other hand, phenylboronic acid (**38**) was reacted with bromobenzene (**39**) using the Suzuki-Miyaura reaction (Figure 13) in the presence of a bidentate ligand ((E)-2-(phenyl(phenylamino)methylene)benzofuran-3(2H)-one) and $PdCl_2$ under assisted-microwave irradiation to form the biphenyl (**40**).[xvii]

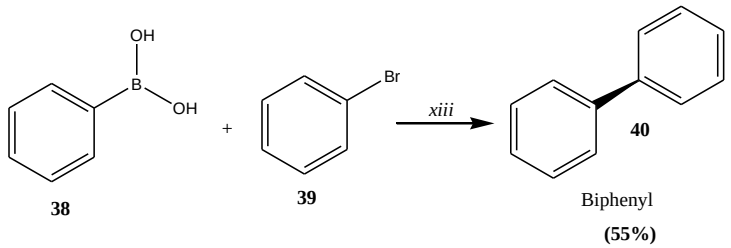



Figure 13. Synthesis of biphenyl (**40**). *Conditions and Reagents*: *xii* = $PdCl_2$, bidentate ligand, $K_2CO_3$, *i*-PrOH, MW (70 $^oC$), 10 min.

Bhosale and coworkers (2024) reported the preparation of compound 7-but-2-ynyl-1-methyl-8-(4-methylene-1-piperidyl)-4,5-dihydro-3*H*-purine-2,6-dione (**43**) from 8-bromo-7-but-2-ynyl-1-methyl-4,5-dihydro-3*H*-purine-2,6-dione (**41**) and 4-methylenepiperidine using the BrettPhos Pd G3 reagent as a catalyst under assisted-microwave irradiation (Figure 14).[xviii]

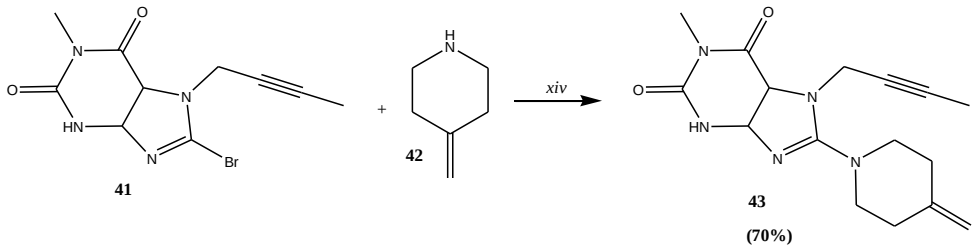



Figure 14. Synthesis of a purine-2,6-dione derivative (**43**). *Conditions and Reagents*: *xiv* = BrettPhos Pd G3, *t*-butanol, MW (80 $^oC$), 1 min.

Besides, a study displays the reaction of compound 7-methyl-2-methylsulfanyl-4-(m-tolyl)-6-phenyl-pyrrolo[2,3-d]pyrimidine (**44**) with (4-methoxyphenyl)boronic acid (**45**) to synthesize the compound 2-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(m-tolyl)-7H-pyrrolo [2,3-d]pyrimi- dine (**46**) in the presence of $Pd(PPh_3)_4$ under microwave irradiation (Figure15).[xix]

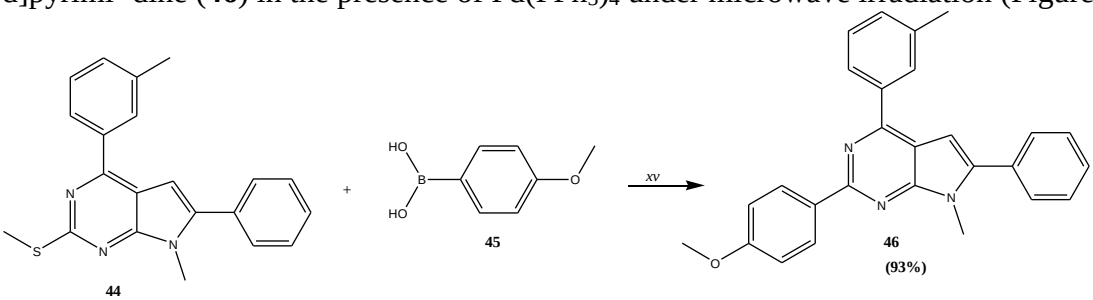



Figure 15. Synthesis of a pyrimidine derivative (**46**). *Conditions and Reagents*: *xiv* = $Pd(PPh_3)_4$, CuMeSal, THF, MW (100 $^oC$), 1 h.

Che and Xu (2011) reported the preparation of 2-methoxy-8-nitro-dibenzofuran (**50**) from 2-bromo-4-methoxy-phenol (**47**) and 1-fluoro-4-nitro-benzene (**48**) under microwave irradiation to afford an intermediate (**49**) via an SNAr reaction, which were then used directly for the subsequent palladium catalyzed intramolecular aryl-aryl coupling (Figure 16).[xx]

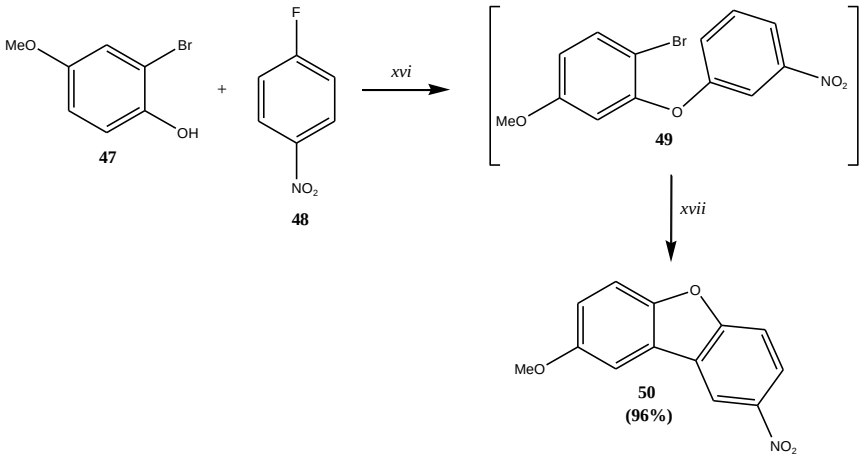



Figure 16. Synthesis of a dibenzofuran derivative (**49**). *Conditions and Reagents*: *xvi* = DMF, $K_2CO_3$, MW (100 $^{O}$C), 10 min; *xvii* = $Pd(OAc)_2$, $K_2CO_3$; DMF, MW (150 $^{O}$C), 10 min.

In addition, Bariwal and co-workers (2010) demonstrated the synthesis of an azatricyclo derivative (**54**) from tert-butyl *tert*-butyl *N*-[2-[2-(2-formylphenyl)-4,5-dimethoxy-phenyl]ethyl]-*N*-[(4-me-thoxyphenyl)methyl]carba-mate (**51**) and p-tolylacetylene (**52**). This reaction involves the formation of compound 2-[4,5-dimethoxy-2-[2-[(4-methoxyphenyl)methylamino]ethyl]- phenyl]benzaldehyde (**53**) as an intermediate followed by an intramolecular cyclization to form **54** (Figure 17).[xxi]

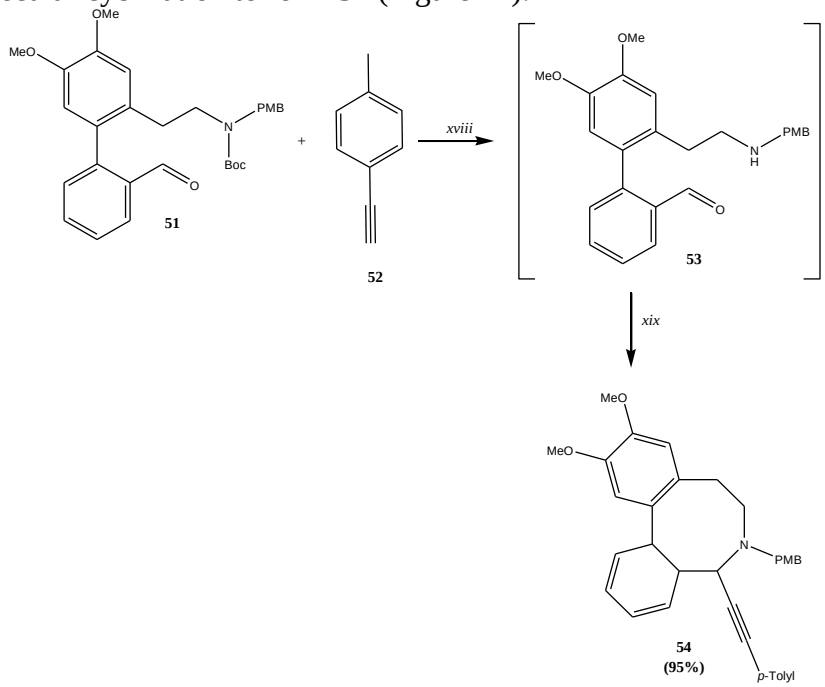



Figure 17. Synthesis of a derivative (**54**). *Conditions and Reagents*: *xviii and xix* = CuBr, toluene, MW(80 W), 100 °C, 15 min.

Finally, a study showed the reaction of 2-bromopyridine (**55**) with morpholine (**56**) to produce the compound 4-(2-pyridyl)morpholine (**57**) in the presence of palladium and a tetrahydropyrimidinium salt using different conditions (Figuer 18 and Table ).

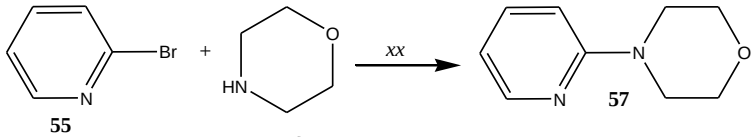



Figure 18. Synthesis of 4-(2-pyridyl)morpholine (**57**). *Conditions and Reagents*: *xx* = base, solvent, MW (150 W), 100 ◦C,

Table. Different conditions involved in the synthesis of 4-(2-pyridyl)morpholine (**57**).

| Entry | Solvent | Base | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | DME | KOH | 20 | 3 |
| 2 | DME | $K_2CO_3$ | 20 | 15 |
| 3 | DME | $Cs_2CO_3$ | 20 | 10 |
| 4 | DME | $^t$BuOK | 20 | 61 |
| 5 | Dioxane | $^t$BuOK | 20 | 58 |
| 6 | DME | $^t$BuOK | 20 | 6 |
| 7 | Toluene | $^t$BuOK | 20 | 19 |
| 8 | DME | $^t$BuOK | 20 | 2 |
| 9 | DME | $^t$BuOK | 20 | 2 |
| 10 | DME | $^t$BuOK | 20 | 27 |
| 11 | DME | $^t$BuOK | 20 | 92 |
| 12 | DME | $^t$BuOK | 60 | 49 |
| 13 | DME | $^t$BuOK | 24 (h) | 30 |

## CONCLUSIONS

This review shows several coupling reactions, particularly the use of different solvents and microwave irradiation conditions. It is noteworthy that these data can be used for decision-making in the development of new compounds.

## ACKNOWLEDGEMENTS

None

## CONFLICT OF INTEREST

The authors declare no conflict of interest

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