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Nickel-catalyzed decarboxylative arylation of azoles with perfluoro- and nitrobenzoates†

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This manuscript describes a Ni-catalyzed method for the direct arylation of azoles using benzoates. Perfluorophenyl and 2-nitrobenzoates participate in these reactions to afford the corresponding products in modest to good yields. The efficiency of the arylations with perfluorobenzoates is highly dependent on both the degree and position of fluorine atoms in the benzoates.

Transition metal catalyzed arylation of aromatic C–H bonds is widely used for the construction of biaryl scaffolds.[1] The vast majority of these transformations entail the coupling of C–H bonds with aryl halides (or pseudohalides) or organometallic reagents. In recent years there has been interest in the development of transformations that replace the halides or organometallic reagents in these arylations with carboxylic acids.[2] The use of carboxylic acids obviates the need for the preparation and use of often sensitive organometallic reagents. Additionally, structurally diverse benzoic acid derivatives are readily available and bench-stable compounds.

Despite these advantages, decarboxylative cross couplings have developed at a relatively slower rate because of the general requirement for harsh conditions for the extrusion of CO_2.[2] The first examples of decarboxylative biaryl bond formation involved the use of Pd catalysis.[2,3] Following these seminal reports, several reports on decarboxylative biaryl formations have been published. Most of these methods employ expensive transition metals such as Pd.[2–4] As such there is an increasing demand for the replacement of noble metals (*e.g.*, Pd) with their earth-abundant counterparts (*e.g.*, Ni).[5–8] To this end, efforts have been made to use Ni catalysts in decarboxylative transformations. However, reports of Ni-catalyzed decarboxylative synthesis of biaryl motifs remain sparse.[9–12] Herein, we describe a method for the Ni-catalyzed intermolecular coupling of perfluorobenzoates with azoles for the synthesis of biaryl compounds. A systematic exploration of the efficiency of these arylations with penta-, tetra- tri- and difluorinated benzoates is presented. These transformations can also be applied toward the coupling of benzoxazoles with 2-nitrobenzoate.

We commenced our studies with the investigation of reaction parameters for the coupling of 5-methylbenzoxazole with pentafluorobenzoate. This reaction serves as a good starting point because Ni-catalyzed C–H activation of acidic C–H bonds in azole substrates has been achieved previously.[9] Furthermore, perfluoroaryl carboxylates are known to extrude CO_2 at moderate temperatures.[13] A plausible mechanism for the proposed Ni-catalyzed C–H arylation based on literature reports of analogous Pd-catalyzed reactions is depicted in Scheme 1.[2] It involves: (i) base-assisted C–H nickelation, (ii) transmetallation between (**I**) and Ar'M (generated upon decarboxylation), (iii) reductive elimination to release the desired product and (iv) oxidation of Ni^0 to regenerate the Ni^{II} catalyst. Importantly, the decarboxylation and oxidation steps are commonly promoted by the addition of Cu or Ag salts in Pd-catalyzed transformations.[2] Furthermore, diglyme has been the solvent of choice for a number of transformations involving decarboxylation of perfluorobenzoate potassium salts.[13]

As such we began our optimizations using the reaction conditions shown in Scheme 2. Several catalysts, oxidants, bases, solvents and temperatures were screened to optimize the yield of the transformation. However, product **1a** is obtained in at most 41% yield. Importantly, only trace amounts (<10%) of **1a** is formed in the absence of $Ni(OTf)_2$ under otherwise optimal conditions suggesting that the Ni catalyst is necessary for the transformation to proceed. The low yield (41%) of **1a** under the Ni-catalyzed reaction conditions is partly due to the homocoupling of both the azole and the carboxylate substrates under the reaction conditions. These observations are consistent with a fundamental challenge associated with decarboxylative C–H arylations. Striking the optimal balance between the relative rates of C–H metallation (Scheme 1, step i) and the

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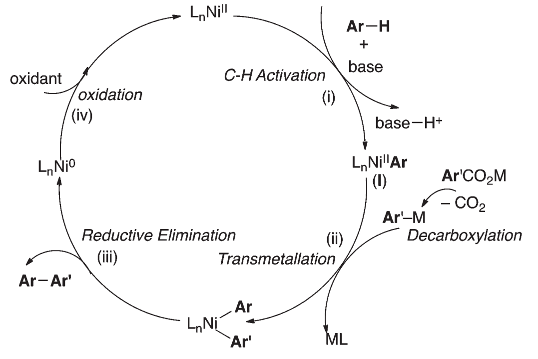
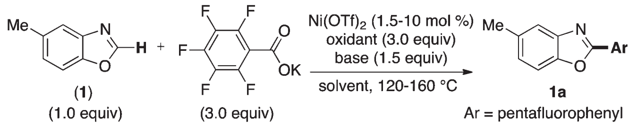


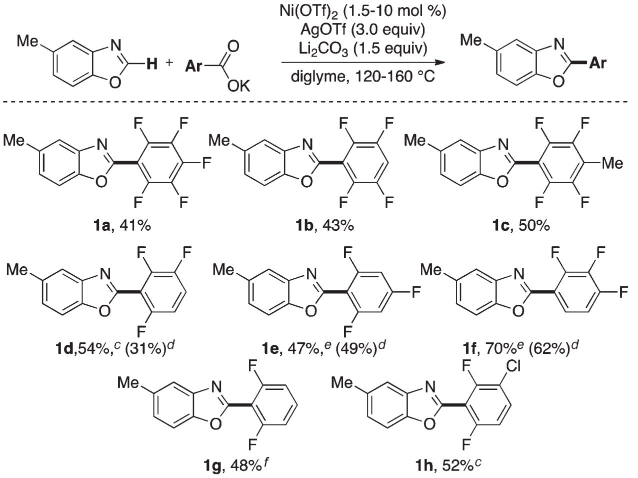
Scheme 1 Plausible mechanism for C–H arylation.



Catalysts, oxidants, bases, solvents and temperatures screened

nickel catalysts	oxidants	bases	solvents
$NiCl_2(PCy_3)_2$	Ag_2CO_3	Li_2CO_3	diglyme
$NiBr_2(DME)$	AgOAc	Rb_2CO_3	DMA
$Ni(acac)_2$	$AgBF_4$	Cs_2CO_3	DMF
$Ni(OAc)_2$	$AgPF_6$	K_2CO_3	xylene
$Ni(OTf)_2$	AgOTf	K_3PO_4	DMA/diglyme
	benzoquinone		

Scheme 2 Optimization of decarboxylative arylation.



Scheme 3 Scope of perfluorobenzoates: [a,b]Conditions: azole (1.0 equiv.), benzoate (3.0 equiv.), $Ni(OTf)_2$ (0.015 equiv.), AgOTf (3.0 equiv.), Li_2CO_3 (1.5 equiv.), diglyme, 120 °C, 20 h. Isolated yields. [c] General conditions with DMA/diglyme (1 : 4 v/v) as solvent. [d] Calibrated GC yields against hexadecane as the internal standard using general conditions but in DMA/diglyme (1 : 4 v/v) as solvent, 10 mol% $Ni(OTf)_2$ and at 160 °C. [e] General conditions with 5 mol% $Ni(OTf)_2$, DMA/diglyme (1 : 4 v/v) as solvent at 160 °C. [f] General conditions with 10 mol% $Ni(OTf)_2$, DMA/diglyme (1 : 4 v/v) as solvent at 140 °C.

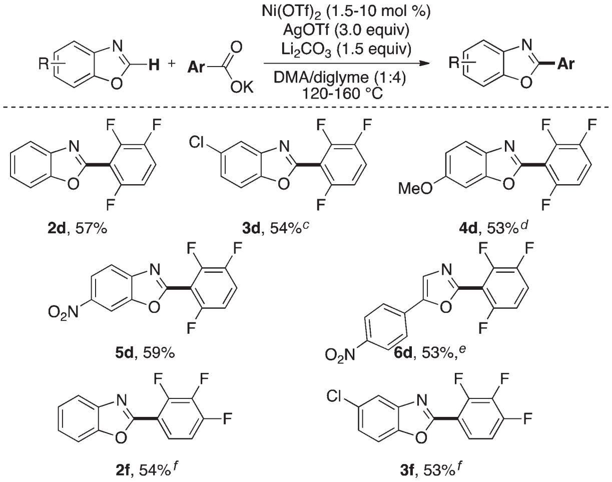
decarboxylation (Scheme 1, step ii) is essential toward preventing the undesired homo-coupling of the aryl-metal intermediates generated upon C–H nickelation (**I**) and decarboxylation (Ar'M) (Scheme 1). Previous reports on Pd and Cu-catalyzed decarboxylative couplings suggest that the relative rate of decarboxylation is highly dependent on the electronic nature of the carboxylate.[2,13] As such, we next explored the use of diverse perfluorobenzoates under the optimal conditions for the formation of **1a**.

As shown in Scheme 3, tetra-, tri- and difluorinated salts participate in this transformation to afford the corresponding perfluorobiaryl products. The temperature and the solvent were optimized for each salt individually. The efficiency of the transformation is highly dependent on both the degree of fluorination and the relative positions of the fluorine atoms in the carboxylate salts. For example the trifluorinated product **1f** is obtained in higher yields than the tetra and pentafluorinated products **1a** and **1b**. Furthermore, under the same reaction conditions (catalyst loading, temperature and solvent) the 2,3,4-trifluorobenzoate salt affords the corresponding biaryl (**1f**) in higher yield than the 2,3,6- and 2,4,6-trifluorobenzoate salts (*cf.* yields in parentheses). Notably, the chlorinated product **1h** is also obtained in modest yield. The C–Cl bond in **1h** can be further elaborated using a myriad of known cross-coupling reactions.[14]

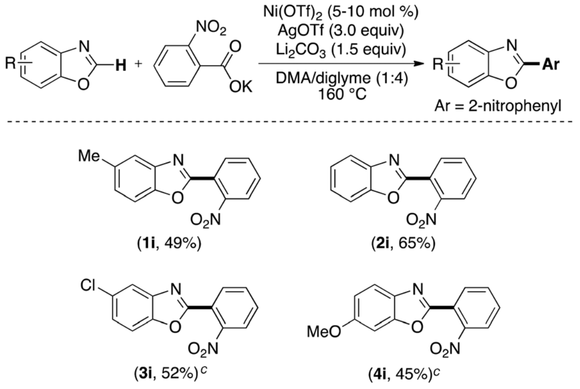
The reaction conditions for these transformations represent an advance over prior methodology.[10] The optimal temperature for the formation of most products (**1a–1d** and **1h**) in Scheme 3 is 120 °C, which is significantly lower than the temperature (170 °C) used to obtain similar products from the corresponding carboxylic acids in place of potassium benzoates.[10] Additionally, the transformation proceeds in the absence of any added ligands to afford products in comparable yields to those reported previously using N-heterocyclic carbene ligands.[10] Furthermore, the temperatures (120–160 °C) of the reactions described herein are at or below the boiling point of the solvent which makes this methodology more synthetically convenient and safer than the previous report which employs (trifluoromethyl)benzene (b.p. = 102 °C) at 170 °C.[10]

As detailed in Scheme 4, the optimal conditions for the arylation of 5-methylbenzoxazole can be applied toward the use of other substituted azoles. Electron-rich (*e.g.*, OMe) and electron-deficient substituents (*e.g.*, NO_2) are compatible with the transformation. Additionally, products bearing aryl chloride groups are obtained in modest yields. The perfluorinated biaryl motifs obtained using this methodology are prevalent in numerous pharmaceutical and material science applications.[15]

Having explored the Ni-catalyzed decarboxylative C–H arylation using perfluorobenzoate salts, we next examined a preliminary scope for the coupling of benzoxazoles with 2-nitrobenzoate (Scheme 5). Analogous to the perfluorobenzoate salts, the 2-nitrobenzoates are known to decarboxylate under thermal conditions.[2] As shown in Scheme 5, the scope of these reactions is similar to the transformations with perfluorobenzoates.



Scheme 4 Scope of azoles: [a,b]Conditions: azole (1.0 equiv.), benzoate (3.0 equiv.), $Ni(OTf)_2$ (0.015 equiv.), AgOTf (3.0 equiv.), Li_2CO_3 (1.5 equiv.), DMA/diglyme (1 : 4 v/v), 120 °C, 20 h. Isolated yields. [c] General conditions with diglyme as solvent. [d] General conditions 5 mol% Ni $(OTf)_2$. [e] General conditions 10 mol% $Ni(OTf)_2$. [f] General conditions with 5 mol% $Ni(OTf)_2$ at 160 °C.



Scheme 5 Coupling with 2-nitropotassiumbenzoate: [a,b]Conditions: azole (1.0 equiv.), benzoate (3.0 equiv.), $Ni(OTf)_2$ (0.05 equiv.), AgOTf (3.0 equiv.), Li_2CO_3 (1.5 equiv.), DMA/diglyme (1 : 4 v/v), 160 °C 20 h. Isolated yields. [c] General conditions with 10 mol% $Ni(OTf)_2$.

Conclusions

In summary, this paper describes an example of Ni-catalyzed arylation of azole C–H bonds using perfluoro- and 2-nitrobenzoate salts. The efficiency of these arylations is highly dependent on the electronic nature of the carboxylate. Further explorations will focus on expanding the scope of these transformations. Additionally, efforts will be made to replace the use of silver triflate with less expensive oxidants in these transformations.

Acknowledgements

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