Current Literature

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Beomjun Joo

Diversity Synthesis via C-H Bond Functionalization: Concept-Guided Development of New C-Arylation Methods for Imidazoles

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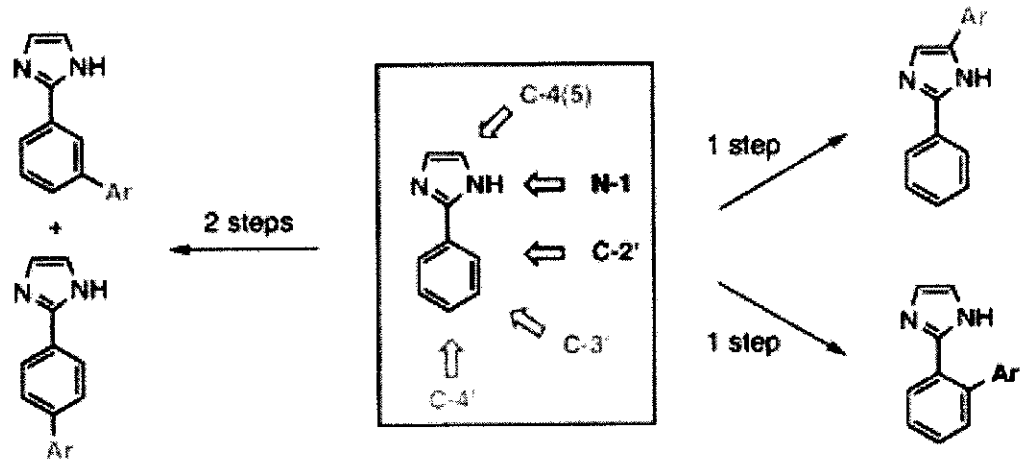


Key Word : Selective C-Arylation of 2-phenyl Imidazole

1. Concept

- Direct and selective introduction of a new functionality (or a new C-C bond) via C-H bond functionalization; one of the hottest issue in organic synthesis
- The impact of C-H bond functionalization may be even greater in the context of diversity synthesis
- This new strategy stands in stark contrast to traditional approaches, which require multistep and often distinct schemes for each derivative
- The concept of comprehensive elaboration of structural motifs serves to systematically expose unsolved and important synthetic challenges.

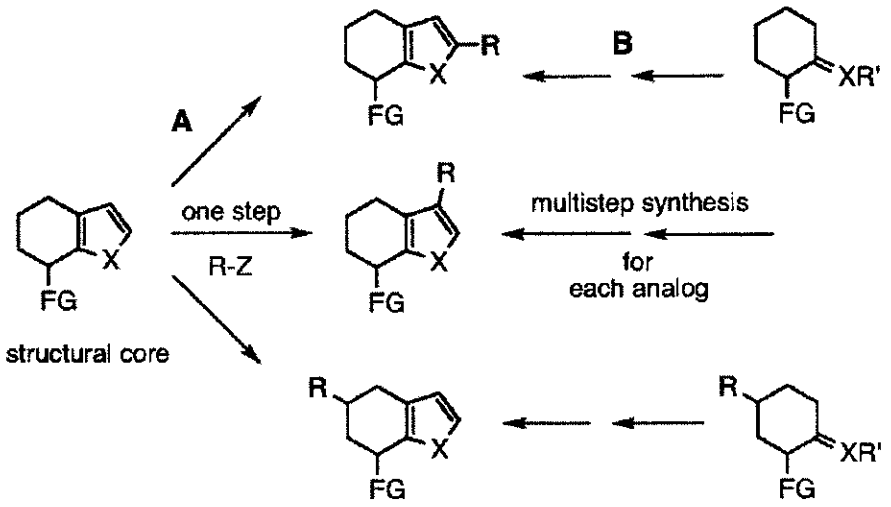


Figure 1 Diversity synthesis via (A) C-H bond functionalization versus (B) traditional methods.

Note) Authors prefer the term "C-H bond functionalization" to the term "C-H bond activation" unless a clear mechanism is present.

2. Systematic Arylation of the 2-Phenylimidazole Core

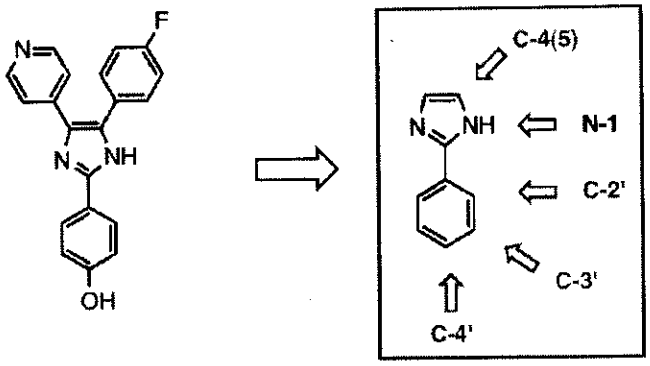


Figure 2 A pharmaceutical lead (SB 202190) inspired the selection of the 2-phenylimidazole motif

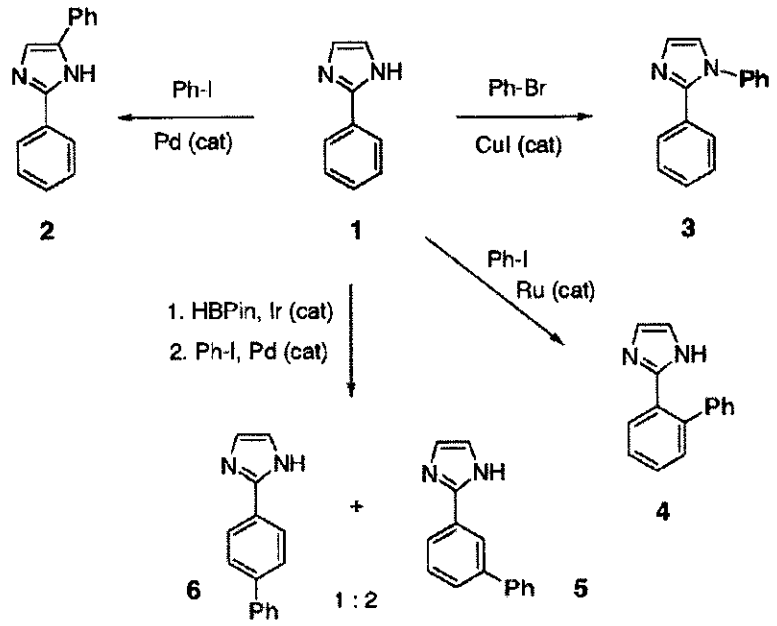
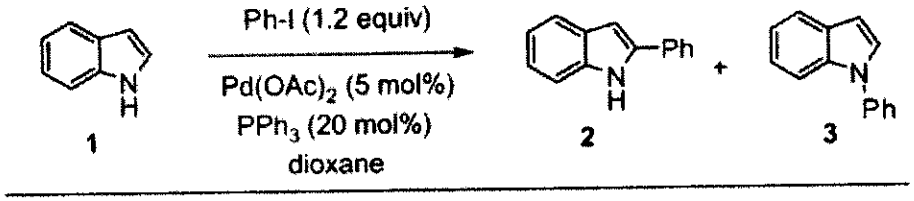


Figure 3 Programmable and comprehensive arylation of the 2-phenylimidazole core

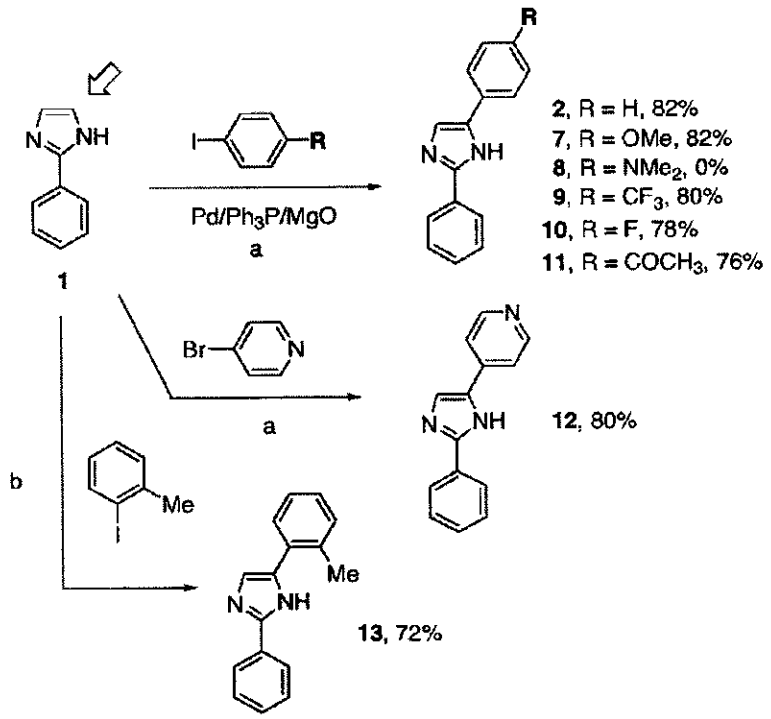
3. **Selective C-4 Arylation of 2-Phenylimidazole.**

Preliminary Report (D. Sames *et al.* JACS 2003, 125, 5274-)



4, X=Br 5, X=OH	BASE (1.2 equiv)	isolated yield (2 / 3)
	LiOH or NaOMe	0 / 0 %
	K_3PO_4 or KOAc	0 / 0 %
	Cs_2CO_3	0 / 5%
	MgO	**53 / 0%**
	EtMgBr[a]	**65 / 0%**
	ZnO	44 / 0%

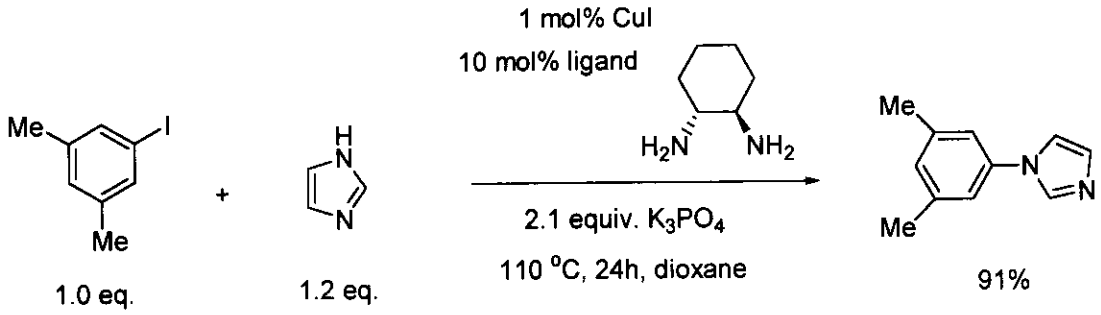
- The selective arylation of C-H bonds may be attributed to the formation of magnesium salts [cf., (XMg-N)-azole] in the presence of MgO



4. Selective N-Arylation and C-2' Arylation of 2-Phenylimidazole

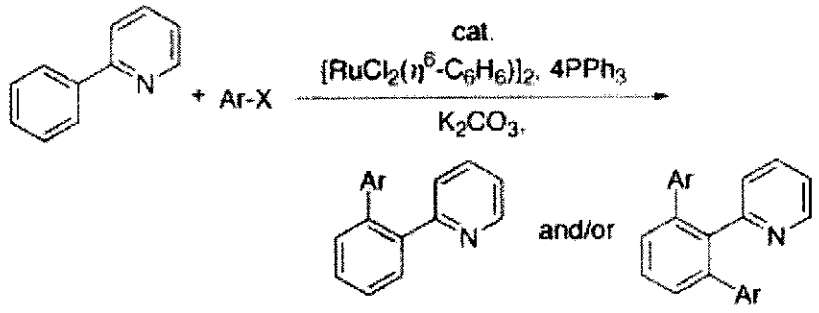
- Several selective N-Arylation of imidazoles has previously been estabilished

Example)



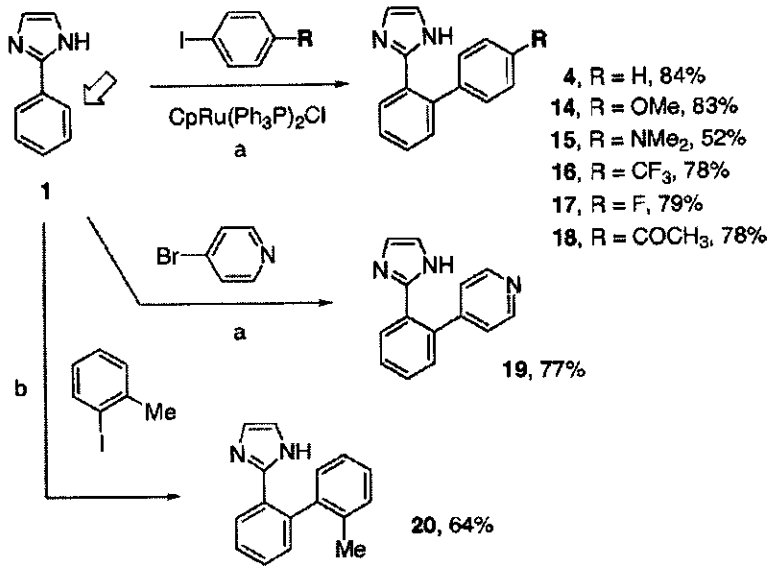
Stephen L. Buchwald *et al*, *J. Am. Chem. Soc.*, 123 (31), 7727 -7729, 2001.

- Preliminary Report for N-directed arylation



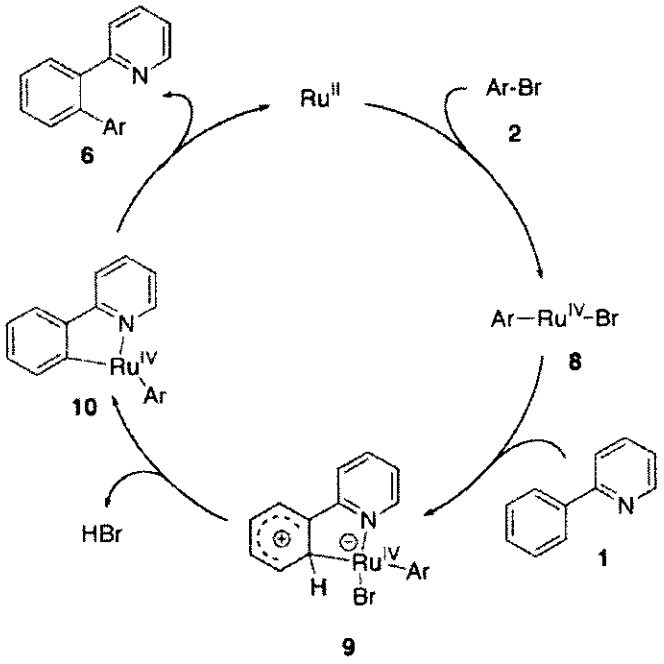
Shuichi Oi *et al, Org. Lett.*, **3** (16), 2579 -2581, 2001.

- Screening of Ru and Rh catalysts: $CpRu(Ph_3P)_2Cl$ being the most efficient catalyst.



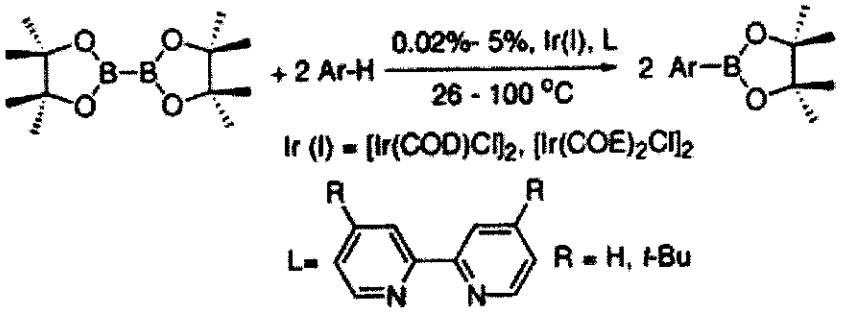
- Reaction Mechanism: Although the mechanism of this reaction remains speculative, the oxidative addition of aryl halide to the ruthenium metal and the cyclometalation represent two key events of the catalytic cycle.

Ex)

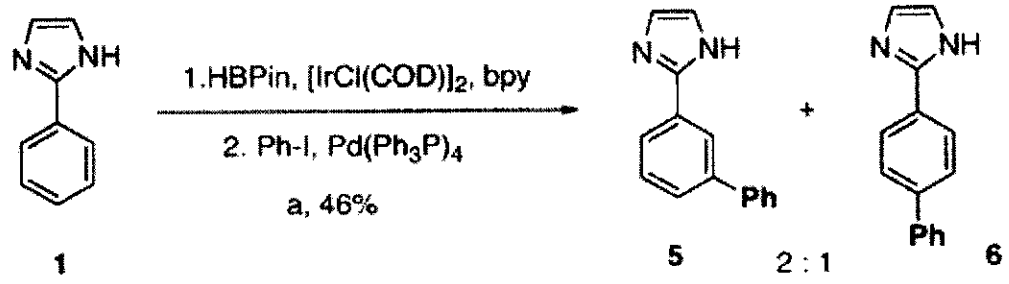


5. C-3' and C-4' Arylation of 2-Phenylimidazole

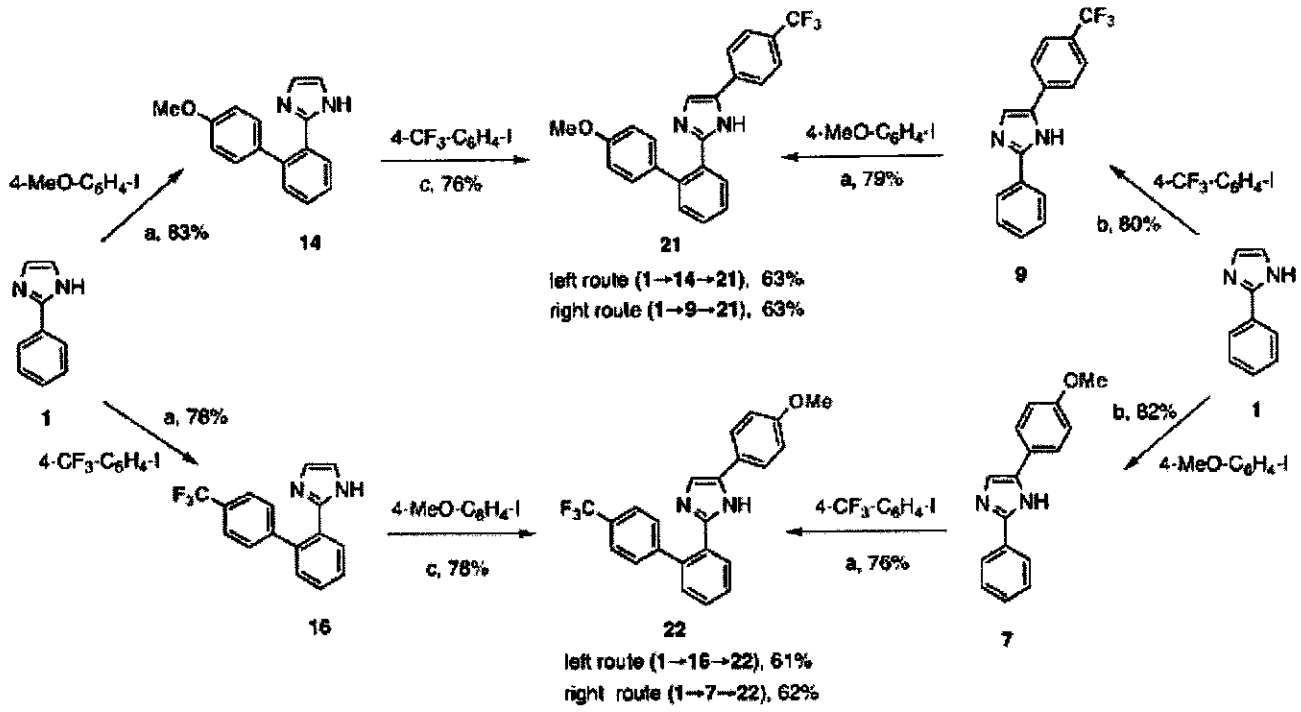
- The application of a two-step procedure, consisting of direct borylation, followed by Suzuki coupling was considered
- The iridium-catalyzed borylation of arenes



J. F. Hartwig et al, J. Am. Chem. Soc.; **2002;** *124*(3) pp 390 - 391

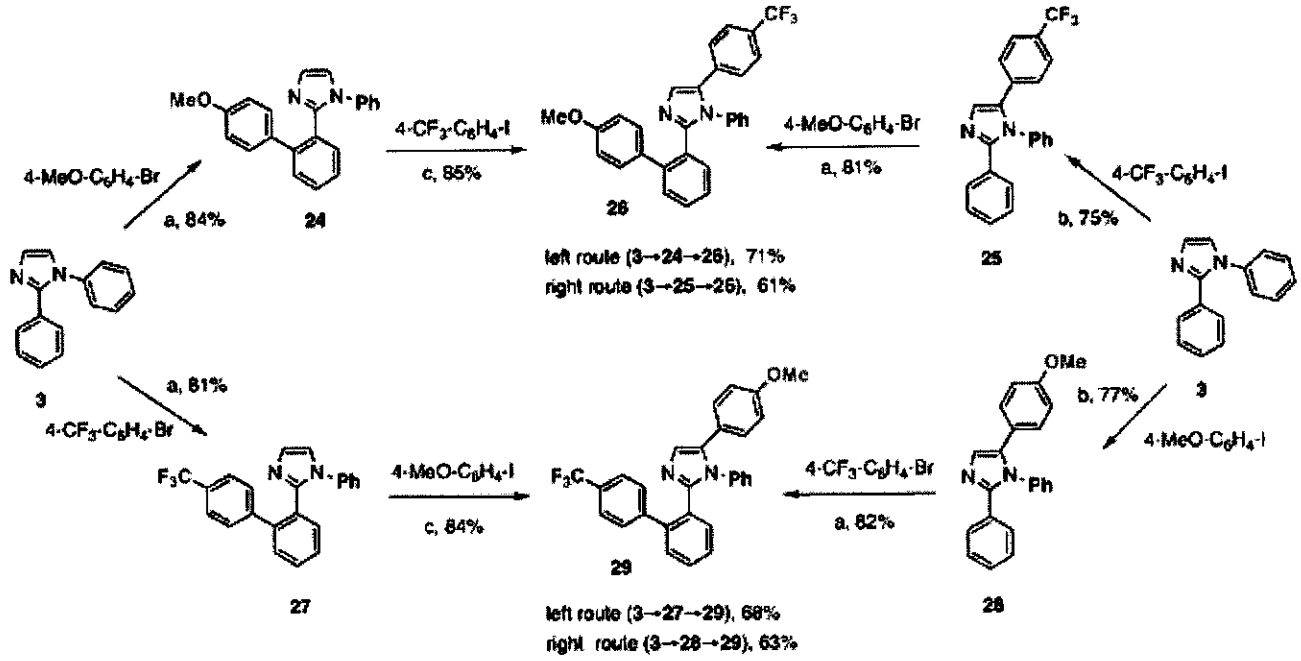


6. Sequential Arylation of 2-Phenylimidazole via Fully Orthogonal Arylation Methods.



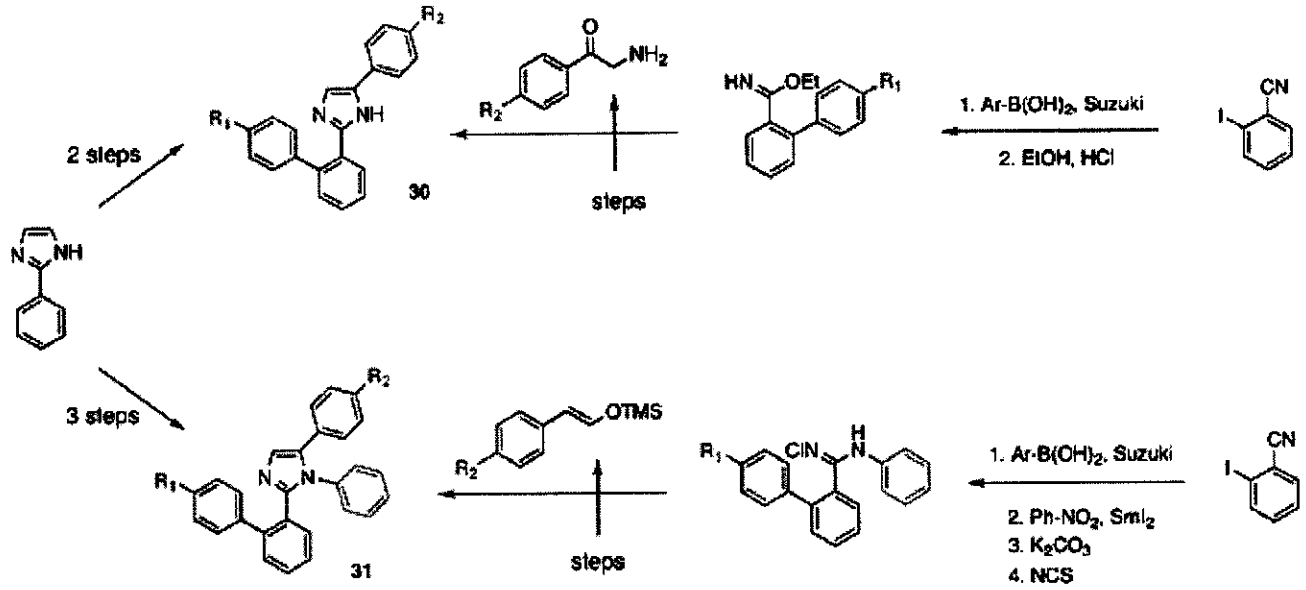
(a) Ar-I (1.8 equiv), $CpRu(Ph_3P)_2Cl$ (5 mol %), Cs_2CO_3 (1.2 equiv), DMF, 130 °C. (b) Ar-I (1.2 equiv), $Pd(OAc)_2$ (5 mol %), Ph_3P (20 mol %), MgO (1.2 equiv), dioxane, 150 °C. (c) Ar-I (1.2 equiv), $Pd(OAc)_2$ (5 mol %), Ph_3P (20 mol %), MgO (1.2 equiv), K_3PO_4 (1.2 equiv), dioxane/DMF, 150 °C.

7. Sequential Arylation of (*N*,2)-Diphenylimidazole



(a) Ar-Br (1.2 equiv), $Rh(acac)(CO)_2$ (5 mol %), Cs_2CO_3 (1.2 equiv), DMF, 150 ° C. (b) Ar-I (1.2 equiv), $Pd(OAc)_2$ (5 mol %), Ph_3P (20 mol %), Cs_2CO_3 (1.2 equiv), DMF, 150 ° C. (c) The same as conditions b except that 1.5 equiv of Ar-I was used.

8. Direct C-H Bond Arylation versus Traditional Syntheses of Imidazole Analog Arrays



Conclusion

- This work formulated the concept of systematic derivatization of a structural motif via C-H bond functionalization.
- This work has shown that systematic and comprehensive arylation of the 2-phenylimidazole core was feasible.
- New arylation methods were developed.
- Direct arylation of positions C-4 and C-2' in 2-phenylimidazole and positions C-5 and C-2' in (*N*,2)-diphenylimidazole was accomplished with complete control of regiochemistry.
- The new methods proved to be orthogonal to one another and applicable to sequential arylation schemes.
- This strategy stands in sharp contrast to the traditional approach, where a distinct and multistep synthesis would be required for each series.
- The development of new methods for direct functionalization of other heteroarenes is currently underway in our laboratories.