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Allylation of Imidazoles. The Beneficial Effect of Imidazole Ligands on (π-Allyl)nickel Coupling

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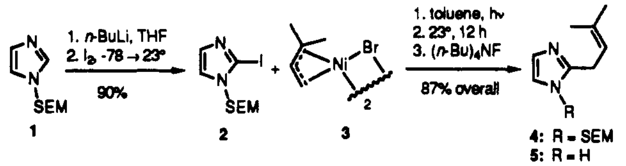
Summary: The coupling of (π-allyl)nickel halide complexes with iodoimidazoles proceeds efficiently in toluene solution without the use of coordinating solvent or added ligand. Nickel-promoted allylation, and symmetrical coupling, of non-imidazole aryl halides is enhanced by using *N*-methylimidazole as an additive.

Methods for elaborating imidazoles by alkylation at C-2 or C-4/5 are potentially useful for the synthesis of ligands,[1] natural products,[2] and drugs.[3] In seeking routes to complex imidazoles for use as ligands,[4] we have experienced difficulties alkylating lithiated imidazoles[5] with prenyl bromide, even though the lithiated imidazoles can be iodinated efficiently. We report that the iodoimidazoles themselves couple efficiently with (π-allyl)nickel reagents *without the use of a polar, coordinating solvent, formerly thought to be essential for this reaction.*[6] Furthermore, *N*-methylimidazole as an additive facilitates both the allylation and symmetrical coupling of aryl halides in toluene solution, and phenyl triflate is coupled efficiently to biphenyl under these conditions.

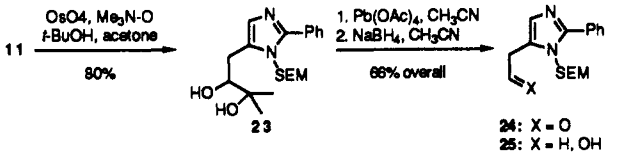
Lithiation of 1-[[2-(trimethylsilyl)ethoxy]methyl]imidazole[7,8] (1) and iodine quench gave SEM-protected 2-iodoimidazole 2. Reaction of 2 with 3 equiv of preformed η^3-prenylnickel bromide dimer[9] (3) in toluene solution occurred upon irradiation[6] for 15 min and then overnight stirring at 23 °C. The coupled product 4 was deprotected[7] at 23 °C to give 2-prenylimidazole 5 in good overall yield.



In contrast to the normal situation for (π-allyl)nickel reactions,[6] no coupling between 2 and 3 occurred in the presence of phosphine ligands or in DMF solution, suggesting that coordination of the imidazole nitrogen to nickel[10,11] is beneficial to, and perhaps necessary for, the overall process in toluene solution.

As shown in Table I, a variety of other iodoimidazoles were coupled in 62–91% yields with preformed 3 or with [η^3-3-(carbomethoxy)allyl]nickel bromide prepared from Ni(cod)$_2$ in situ (entries 5 and 6).[9] Use of prenyl trifluoroacetate[12] with Ni(cod)$_2$ reduced the yield (entry 2). Without the stabilizing influence of the carbomethoxy substituent, allyl-substituted imidazoles (see 22, entry 11) could not be isolated in pure form by chromatography on silica, which may be due in part to their tendency to autooxidize or to isomerize to the conjugated (1-propenyl)-imidazoles.[13] The coupling reaction does not require a basic imidazole nitrogen at the adjacent position; a more distant position also reacts (entries 4, 5, and 10). An iodide at C-2 is more reactive toward coupling than one at C-5 (2,5-diiodo-1-methylimidazole, entry 8); the second iodide may be reduced by NiI that is generated by reduction elimination of coupled product.[6] Imidazole N-protection is not required (entry 9) but appears to be helpful (compare with entries 4 and 7). All of the prenyl imidazoles were quite susceptible to autooxidation (the principal product is the allylic hydroperoxide) and were therefore stored under argon.

To demonstrate the utility of the prenyl substituent, one adduct (11) was oxidized[14] to the diol 23 and then further[15] to the imidazolylacetaldehyde 24. Reduction of 24 gave the corresponding (hydroxyethyl)imidazole 25. These kinds of two-carbon substituents are normally difficult to introduce onto imidazole rings.[16,17]



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[2] For some examples of (alkylated)imidazole-containing natural products see the following. Anosmine: Leander, K.; Luning, B. *Tetrahedron Lett.* **1968**, 905. Diphthamide: Evans, D. A.; Lundy, K. M. *J. Am. Chem. Soc.* **1992**, *114*, 1495. Pilocarpine, leading references: Kim, T. H.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3699. Clathrodine: Morales, J. J.; Rodriguez, A. D. *J. Nat. Proc.* **1991**, *54*, 629. Leuhistin: Yoshida, S.; Naganawa, H.; Aoyagi, T.; Takeuchi, T.; Takeuchi, Y.; Kodama, Y. *J. Antibiot.* **1991**, *44*, 579.

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[11] Addition of 2 equiv of 1-methylimidazole to 1 equiv of 3 in benzene-d_6 solution in the dark caused a shift in the UV spectrum (e.g., the band at 420 nm moves to 430 nm). ^{1}H NMR analysis of the reaction mixture shows signals for Ni-bound 1-methylimidazole at δ 2.38 (s, NCH$_3$), 5.98 (s, H-5), 6.86 (s, H-4), 7.93 (s, H-2).

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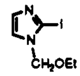
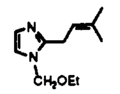
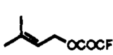
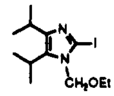
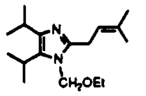
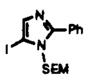
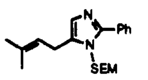
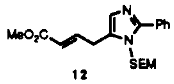
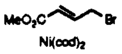
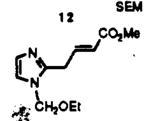
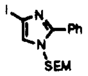
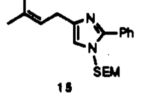
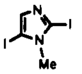
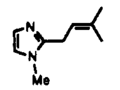
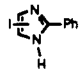
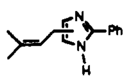
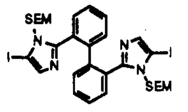
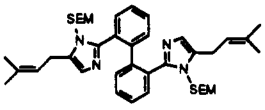
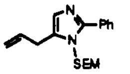
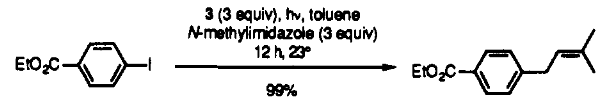
Table I. Allylation of Imidazoles

entry	iodoimidazole	(π-Allyl)nickel	product	yield[a] (%)
1	 6	3	 7	91
2	6	 Ni(cod)$_2$	7	37
3	 8	3	 9	92
4	 10	3	 11	82
5	10	 Ni(cod)$_2$	 12	86
6	6	 Ni(cod)$_2$	 13	90
7	 14	3	 15	73
8	 16	3	 17	86
9	 18	3	 19	74
10	 20	3	 21	51
11	10	 Ni(cod)$_2$	 22	38[b]

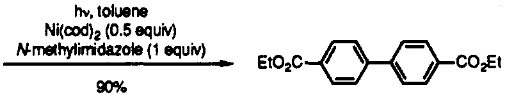
[a] Yield refers to product isolated by silica chromatography unless otherwise specified. [b] Yield refers to crude product characterized by ^{1}H NMR analysis. The product is unstable toward silica.

The mild reaction conditions, high yields, and easy workup associated with the nickel-promoted allylation of imidazoles suggested that other, non-imidazole, coupling reactions should be tried in toluene solution with an appropriate nickel-ligating imidazole added to the reaction mixture. The coupling of **3** with ethyl *p*-iodobenzoate (**26**) at room temperature in toluene solution containing 3 equiv of *N*-methylimidazole gave ethyl 4-prenylbenzoate **27** in nearly quantitative yield; no reaction occurred in the absence of *N*-methylimidazole.



26 27

Several *symmetrical* couplings[18] were also carried out in toluene solution. Coupling of **26** occurred in the presence of 0.5 equiv of Ni(cod)$_2$ and 1 equiv of added *N*-methylimidazole to give diethyl 4,4'-biphenyldicarboxylate (**28**). Phenyl triflate (**29**) gave biphenyl (**30**) when potassium iodide[19] was also present, a reaction that is to our knowledge the first example of nickel-promoted aryl triflate homocoupling. Finally, the hindered,[20] imidazole-bearing aryl bromide **31** gave the useful ligand[4,21] **32** in good yield without need for a coordinating solvent or an added ligand.

26 

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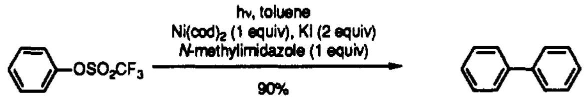
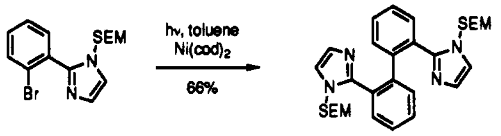


29 30



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Supplementary Material Available: Experimental procedures and spectral data for all new compounds (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[21] This convergent synthesis of **32** constitutes an improvement over the previous route. See ref 4 and: Knapp, S.; Keenan, T. P., Zhang, X.; Fikar, R.; Potenza, J. A., Schugar, H. J. *J. Am. Chem. Soc.* **1990**, *112*, 3452.