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Cross Coupling of Vinyl Triflates and Alkyl Grignard Reagents Catalyzed by Nickel(0)-Complexes

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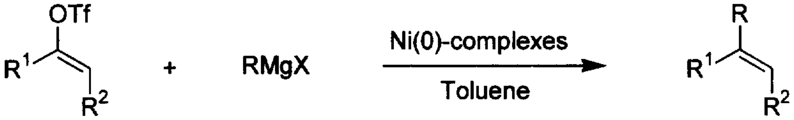
Abstract: The scope and limitations of the Nickel(0)-catalyzed cross coupling of vinyl triflates with alkyl Grignard reagents have been studied. The effect of triflate substitution, solvent, and especially ligands have been examined. Ligands which are successful for sp^2 and sp Grignard reagents fail for sp^3 Grignard reagents. © 1999 Elsevier Science Ltd. All rights reserved.

The cross coupling of Grignard reagents with aryl and alkenyl halides under Ni(0) catalysis has been known since the pioneering research of Kumada[1] and Corriu[2] in 1972. This work has since been expanded upon to include organozinc reagents[3] and halide surrogates such as (aryl) triflates[4], enol phosphonates[5] and silyl enol ethers[6] utilizing both Ni(0) and Pd(0)[7] complexes as catalysts. By comparison, there exists only a single example[4] of the coupling of *vinyl triflates* with Grignard reagents under nickel catalysis.[8] The scope, limitations, and ligand effects of this cross coupling have never been examined and are the subject of this communication.



Our first goal was to explore both cyclic and acyclic triflates[9] including tetrasubstituted species, as shown in Table 1. Indanone triflate **1** (entries 1,2) coupled with both EtMgBr and MeMgBr utilizing $NiCl_2dppp$ in high yield, and both reactions were complete in under one hour at ambient temperature.[10] Tetralone triflate **2** (entries 3-6) also coupled efficiently with alkyl Grignard reagents, although reaction times were somewhat longer, and elevated temperature (55°) was required for BnMgCl. Use of dppb[11] as ligand (entry 5) proved inferior to dppp, as the yield was lowered due to formation of reduced (alkene) material as a side product[12]. Following the protocol of Snieckus *et al.*[4], couplings of **2** with PhMgBr (entries 7,8) were examined. As expected, $Ni(acac)_2$ furnished product **12** in high yield, as did $NiCl_2dppe$. As we shall later show, however, (Table 2), $Ni(acac)_2$ is unsuitable for the coupling of alkyl Grignard reagents, except for MeMgBr which underwent slow coupling with **2** at 55 °C. The styrenyl triflate **3** was found to be a very good substrate for coupling (entries 10-11), while somewhat diminished yields were observed with cycloalkenyl triflate **4** (entry 12). Tetrasubstituted triflate **5** (entry 13) provided a very low yield of adduct with *n*-BuMgCl. In this case, large amounts of unreacted triflate and reduction products were observed.

The use of *secondary* alkyl Grignard reagents is complicated by competing formation of *n*-alkyl and reduction side products[7]. We thus chose to examine this cross coupling more closely to determine the optimum ligands for product formation. Triflate **2** and *i*-PrMgCl were utilized for this study, and the results are shown in Table 2. In all cases, the reactions were quenched after one hour at 55°, and the product distribution determined by ^1H NMR. Two ligands with large bite angles[7], dppf and dppb, were examined first (entries 1,2) and found to fail completely, as only unreacted starting material was observed. A critical observation was made in the use of the weak ligand acac (entry 3). Only unreacted starting material and reduction product were observed. It is thus clear that *acac, which readily couples aryl Grignard reagents, does not support cross coupling of sp^3 Grignard*

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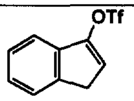
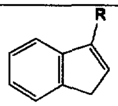
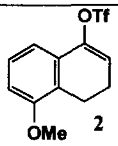
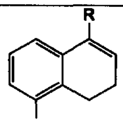
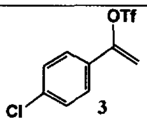
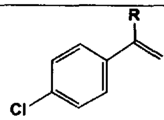
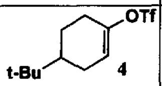
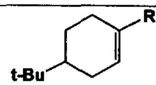
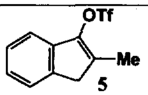
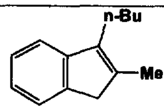
reagents. Use of the monodentate ligand PPh_3 (entry 4) was also unsuitable. The COD ligand was only marginally better, where a small amount of desired product was accompanied by triflate **2** and reduced material.

Our results improved as we moved to dppp and dppe, two ligands with smaller bite angles (entries 6,7). Use of dppp gave the *i*-Pr adduct as the major product, although the *i*-Pr/*n*-Pr ratio (3:1) was still low. The highest ratio (8:1) and the least amount of reduced material was obtained in toluene with dppe as ligand. With these results in hand, we then examined these two ligands in THF rather than toluene (entries 8,9). Optimum results were obtained for dppe where the *i*-Pr/*n*-Pr ratio of 14:1 was observed, along with 20% reduced material. However, the reaction was clearly more sluggish in THF.

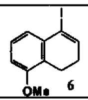
Table 1. Cross Coupling of Vinyl Triflates and Grignard Reagents.

Entry	**Triflate**	**RMgX**	**Conditions**[a]	**Time**	**Product**	**Yield**[b]
1	 **1**	EtMgBr, 3 eq.	$NiCl_2$dppp, C_6H_6	20 min. rt	 **7, R=Et**	91%
2	**1**	MeMgBr, 3 eq.	$NiCl_2$dppp, C_6H_6	20 min. rt	**8**, R=Me	91%
3	 **2**	MeMgCl, 1.5 eq.	$NiCl_2$dppp, PhMe	3h rt	 **9, R=Me**	95%
4	**2**	EtMgBr, 1.5 eq.	$NiCl_2$dppp, PhMe	2.5h rt	**10**, R=Et	90%
5	**2**	EtMgBr, 1.5 eq.	$NiCl_2$dppb, PhMe	2.5h rt	**10**, R=Et	65%[c]
6	**2**	BnMgCl, 1.5 eq.	$NiCl_2$dppp, PhMe	4h 55°	**11**, R=Bn	87%
7	**2**	PhMgBr, 2 eq.	$NiCl_2$dppe, PhMe	2h rt	**12**, R=Ph	76%
8	**2**	PhMgBr, 2 eq.	$Ni(acac)_2$, PhMe	2h rt	**12**, R=Ph	80%
9	**2**	*n*-PrMgCl, 3 eq.	$NiCl_2$dppp, PhMe	1.5h 55°	**13**, R=*n*-Pr	93%
10	 **3**	*n*-BuMgCl, 1.25 eq.	$NiCl_2$dppp, PhMe	30 min. rt	 **14, R=n-Bu**	84%
11	**3**	BnMgCl, 1.3 eq.	$NiCl_2$dppe, PhMe	45 min. rt	**16**, R=Bn	85%
12	 **4**	*n*-BuMgCl, 2 eq.	$NiCl_2$dppe, C_6H_6	2h rt	 **17, R=n-Bu**	75%
13	 **5**	*n*-BuMgCl, 3 eq.	$NiCl_2$dppp, PhMe	2h 55°	 **18**	24%

a) 5 mol% b) isolated yields after chromatography. c) 30% reduced material formed.

These results are largely in concert with earlier work[1] on Ni(0)-catalyzed couplings of Grignard reagents with *aryl chlorides* where dppp (and to a lesser extent dppe) was found to be a superior ligand. In contrast, the coupling of secondary alkyl Grignard reagents with aryl halides under *Pd(0)* catalysis[7] was found to proceed optimally with the large bite angle ligand dppf, while dppe was completely inactive. Since no ligand optimization studies for triflate couplings with Grignard reagents have ever been reported, it was unclear whether the present results reflected differing ligand requirements for the two metals or simply a difference in the two electrophilic partners. To address this issue, we prepared[13] the vinyl iodide analogue **6** to triflate **2** and studied its cross coupling as shown in Table 2. The results obtained largely parallel those observed with triflate **2**, as dppf, acac, COD, dppb and PPh$_3$ (entries 12-16) were found to be poor ligands for the reaction. Use of dppp and dppe were far superior, and dppe in PhMe provided the *i*-Pr adduct uncontaminated by the *n*-Pr isomer. As further confirmation of these results, we also performed one cross coupling of triflate **2** using *PdCl$_2$dppf* and observed (entry 10) a very high *i*-Pr/*n*-Pr ratio. The ligand which was optimum for nickel, dppe, was found to be a poor ligand for palladium (entry 11).

Table 2. Cross Coupling of Triflate 2 and Iodide 6 with *i*-PrMgCl.

Entry^{a}	Substrate	Catalyst^{b}, solvent	*i*-Pr:*n*-Pr	Results
1	**2**	NiCl$_2$dppf, PhMe	NA	No reaction
2	**2**	NiCl$_2$dppb, PhMe	NA	No reaction
3	**2**	Ni(acac)$_2$, PhMe	NA	**2** + 25% reduced material
4	**2**	NiCl$_2$(PPh$_3$)$_2$, PhMe	NA	**2** + 40% reduced material
5	**2**	Ni(COD)$_2$, PhMe	NA	**2**, 35% product + 40% reduced
6	**2**	NiCl$_2$dppp, PhMe	3 : 1	30% reduced material
7	**2**	**NiCl$_2$dppe, PhMe**	**8 : 1^{d}**	<5% reduced material
8	**2**	NiCl$_2$dppp, THF^{c}	10 : 1	70% reduced material
9	**2**	**NiCl$_2$dppe, THF^{c}**	**14 : 1**	20% reduced material
10	**2**	**PdCl$_2$dppf, PhMe**	**> 20 : 1**	**<5% reduced material**
11	**2**	**PdCl$_2$dppe, PhMe**	**3 : 1**	50% **2** + 10% reduced material
12	 6	NiCl$_2$dppf, PhMe	NA	**6** + 50 % reduced material
13	**6**	Ni(acac)$_2$, PhMe	NA	Reduction only
14	**6**	Ni(COD)$_2$, PhMe	NA	Reduction only
15	**6**	NiCl$_2$dppb, PhMe	NA	10% product, 90% reduced
16	**6**	NiCl$_2$(PPh$_3$)$_2$, PhMe	NA	Reduction only
17	**6**	NiCl$_2$dppp, PhMe	6 : 1	50% reduced
18	**6**	**NiCl$_2$dppe, PhMe**	**> 20 : 1**	**<5% reduced material**

a) All rxns. 1h 55°, 2 eq. RMgX unless otherwise noted b) 5 mol% c) 4 eq. RMgX d) RMgX added over 1h

It is thus clear that *for the specific case of the coupling of sp^3 Grignard reagents with vinyl triflates*, the use of bidentate ligands with a small bite angle is a fundamental requirement of Ni(0)[14] for these reactions. The results are independent of the nature of the electrophile. Similarly, the use of a large bite angle ligand for Pd(0)[15] in this reaction is a fundamental property of the metal, equally independent of the electrophile.

In summary, we have found that trisubstituted triflates couple readily with sp^3 Grignard reagents, yet tetrasubstituted substrates react poorly, if at all. Weak ligands such as acac, which support coupling of aryl Grignard reagents, fail in the case of alkyl Grignard reagents. In all cases, the use of bidentate ligands with small bite angles are necessary for optimized yields, in contrast to the analogous Pd(0) catalyzed reactions. This is especially true in the case of secondary alkyl Grignard reagents, where the use of dppe in THF was found to drastically reduce the amount of the *n*-alkyl side product.

References:

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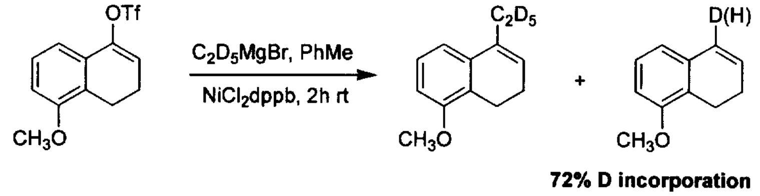
4. Snieckus, V.; Sengupta, S.; Leite, M., Raslan, D.S.; Quesnelle, C.A. *J. Org. Chem.* **1992**, *57*, 4066.
5. Claesson, A.; Sahlberg, C.; Quader, A. *Tetrahedron Lett.* **1983**, *24*, 5137.
6. Kumada, M.; Hayashi, T.; Katsuro, Y. *Tetrahedron Lett.* **1980**, *21*, 3915.
7. Hayashi, T.; Higuchi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.
8. For examples using manganese catalysis, see Fugami, K.; Oshima, K.; Utimoto, K. *Chemistry Lett.* **1987**, 2203.
9. The triflates were prepared following the procedure in Stang, P.J.; Treptow, W. *Synthesis* **1980**, 283.
10. **General procedure.** To a solution of 4'-chloro-1-trifluoromethanesulfonato-styrene (290 mg, 1.0 mmol) in 5 ml toluene (Aldrich anhydrous) in a 20 ml headspace vial (Kimble or Wheaton) with a stirbar was added $NiCl_2dppp$ (28 mg, 0.05 mmol). The vial was sealed with a septum and briefly evacuated/filled with argon 3-4 times. BuMgCl[16] (2.03M in THF, 616 μl, 1.25 mmol) was added at room temperature and the reaction was stirred for 30 min at rt when TLC showed complete reaction. The mixture was quenched by addition of 5 ml saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with water, brine and dried over $MgSO_4$ to give 228 mg yellow oil after evaporation of the solvent. The oil was purified on silica using hexanes as the eluent ($R_f = 0.7$) to afford 163 mg (84 %) pure product as a colorless oil.

    ^{1}H-NMR(400 MHz, $CDCl_3$): 7.31-7.40 (m, 4H), 5.28 (s,1H), 5.11 (s,1H), 2.51 (t, *J*=7.5Hz, 2H), 1.30-1.50 (m, 4H), 0.94 (t, *J*=7.3Hz, 3H). **^{13}C-NMR**(100 MHz, $CDCl_3$): 148.05, 140.32, 133.40, 128.78, 127.86, 112.98, 35.40, 30.76, 22.77, 14.32. **GCMS, m/z:** 194(2), 152(100), 137(10), 117(20), 115(20).
11. $NiCl_2dppb$ was prepared according to Frauenrath, H.; Wille, A.; Tomm, S. *Synthesis* **1998**, 305.
12. We have briefly investigated the mechanistic origin of the reduced materials in these cross couplings with poor ligands. When C_2D_5MgBr (from C_2D_5Br and Mg(0)) was coupled with triflate **2** as shown, 72%D incorporation was found in the reduced species (reproducible, 2 experiments). Thus, the majority of the reduction occurs *via*



    β-hydride elimination. Experiments using deuterated solvents, however, have not shown label incorporation, and the source of the remaining reduction is unknown.
13. Barton, D.H.R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron* **1988**, *44*, 147.
14. The bite angle for $NiCl_2dppe$ is 87.3°, see Busby, R.; Hursthouse, M.B.; Jarret, P.S.; Lehmann, C.W.; Abdul Malik, K.M.; Phillips, C. *J. Chem. Soc. Dalton Trans.* **1993**, 3767.
15. The bite angle for $PdCl_2dppf$ is 99.1°, see reference 7.
16. Titration was performed according to Kofron, W.G.; Baclawski, L.M. *J. Org. Chem.* **1976**, *41*, 1879.