Homogeneous Catalysis

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Hiyama Reactions of Activated and Unactivated Secondary Alkyl Halides Catalyzed by a Nickel/Norephedrine Complex**

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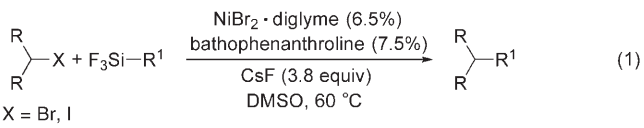
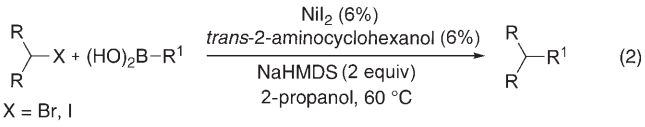
We recently reported that a nickel/bathophenanthroline-based catalyst accomplishes Hiyama couplings[1] of unactivated secondary alkyl electrophiles for the first time [Eq. (1), DMSO = dimethyl sulfoxide].[2] Although this represented a



(1)

step forward in the expansion of the scope of metal-catalyzed cross-coupling reactions,[3,4] it was not an ideal solution from at least three standpoints: First, the yields of the Hiyama reactions were moderate (60–82%); second, the method was not generally effective for activated secondary alkyl halides; and third, only bipyridine-type ligands that lack a substituent *ortho* to the nitrogen atom furnished useful catalysts (that is, bathophenanthroline, 1,10-phenanthroline, and 2,2′-bipyridine, but not neocuproine). This sensitivity to substitution represented a significant impediment to our long-term goal of achieving asymmetric Hiyama reactions, since virtually all of the effective chiral bipyridines that have been described have groups in the *ortho* position.[5]

In 2006 we reported that an amino alcohol can serve as a useful ligand for cross-coupling reactions of unactivated alkyl electrophiles [Suzuki coupling reactions: Eq. (2), HMDS = 1,1,1,3,3,3-hexamethyldisilazane].[6] Unfortunately, when we

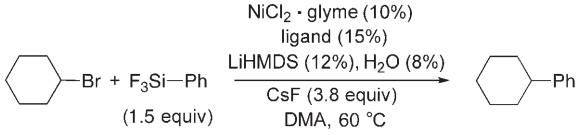


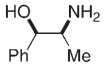
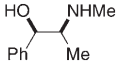
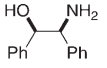
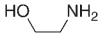
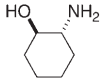
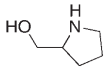
(2)

attempted a Hiyama reaction with *trans*-2-aminocyclohexanol [cyclohexyl bromide and F_3SiPh, Eq. (1)], we obtained none of the desired cross-coupling product.

Despite this initial discouraging result, we recognized that a diverse array of amino alcohols are readily (and commercially) available, and we decided to explore the possibility that one such ligand might enable us to address the shortcomings of our first-generation catalyst for Hiyama reactions of alkyl halides. After considerable effort, we were pleased to determine that, in the presence of norephedrine, we can achieve the cross-coupling of cyclohexyl bromide with F_3SiPh in very good yield (Table 1, entry 1).[7] As illustrated in Table 1, the structure of the amino alcohol plays a critical role in determining the efficiency of the Hiyama reaction. Thus, substituents on the nitrogen atom (Table 1, entry 2) and changes in the groups on the two-carbon tether (Table 1, entries 3 and 4) had a significant impact on catalyst activity. The two amino alcohols that we had employed in our earlier investigation of the Suzuki reaction[2] provided only modest yields in Hiyama cross-coupling reactions under these conditions (Table 1, entries 5 and 6).[8]

Table 1: Hiyama reactions of alkyl halides: effect of the amino alcohol ligand.[a]



Entry	Ligand	Yield [%][b]
1		89
2		15
3		14
4		74
5		47
6		53

[a] DMA = *N*,*N*-dimethylacetamide. [b] Yield determined from GC analysis against a calibrated internal standard (average of two experiments).

The nickel/norephedrine catalyst could be applied to Hiyama reactions of a variety of unactivated secondary alkyl bromides (Table 2, entries 1–8).[9] As indicated in Table 2, this method typically gave significantly higher yields than the previously reported bathophenanthroline-based catalyst. Both cyclic (Table 2, entries 1–5) and acyclic (entries 6–8)

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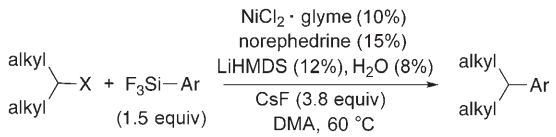
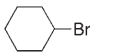
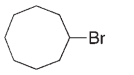
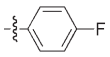
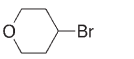
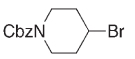
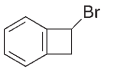
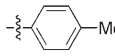
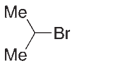
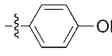
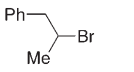
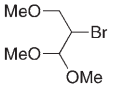
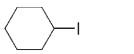
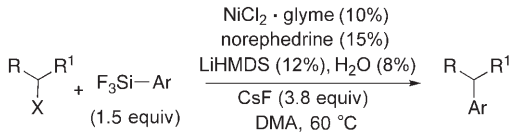
Table 2: Nickel/norephedrine-catalyzed Hiyama reactions of unactivated alkyl halides.[a]

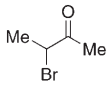
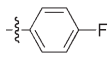
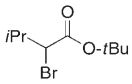
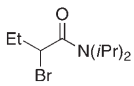
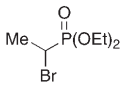
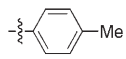
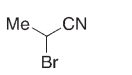
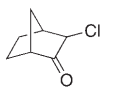
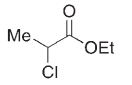
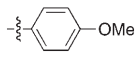
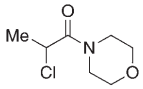
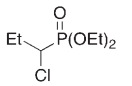
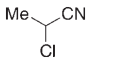


Entry	Alkyl halide	Ar	Yield [%][b]
1			88
2			59
3			85
4			82
5			89[c]
6			76[c]
7			65
8			86
9			94

[a] Cbz = benzyloxycarbonyl. [b] Yield of isolated product (average of two experiments). [c] Purity of product: 97%.

Table 3: Nickel/norephedrine-catalyzed Hiyama reactions of activated alkyl halides.



Entry	Alkyl halide	Ar	Yield [%][a]
1			78
2			82
3			83
4			92
5			76
6			80[b]
7			84
8			86
9			60
10			88
11			76

[a] Yield of isolated product (average of two experiments). [b] 1:1 mixture of diastereomers.

alkyl bromides were found to cross-couple with an array of aryl silanes. The catalyst tolerated a range of functional groups (Table 2, entries 2–4 and 6–8) and could be employed, without modification, in Hiyama coupling reactions of unactivated secondary alkyl iodides (Table 2, entry 9).

Although the original nickel/bathophenanthroline catalyst [Eq. (1)] could achieve Hiyama reactions of unactivated secondary alkyl bromides and iodides, it was found to be generally not effective for cross-coupling reactions of activated halides, perhaps as a result of the propensity of the oxidative-addition adduct to undergo β-hydride elimination to produce a conjugated olefin. Indeed, to the best of our knowledge, there are no reports of Hiyama couplings of activated secondary alkyl electrophiles.

The nickel/norephedrine-based catalyst addresses this gap in the methodology: thus, the conditions that we had developed for Hiyama reactions of unactivated secondary alkyl halides (Table 2) could be applied directly to cross-coupling reactions of a range of activated electrophiles (Table 3).[10] For example, α-brominated ketones, esters, amides, phosphonates, and nitriles were suitable coupling partners (Table 3, entries 1–5).[11] Interestingly, the standard reaction conditions could also be employed for Hiyama cross-coupling reactions of activated alkyl chlorides, including an allylic chloride (Table 3, entries 6–11). As far as we are aware, there is no precedent for a Hiyama coupling of an alkyl chloride.

In summary, we have established that a nickel/amino alcohol based catalyst provides the most efficient and versatile method that has been described to date for Hiyama reactions of secondary alkyl electrophiles. Not only unactivated, but also activated, halides can be employed as coupling partners. In addition to cross-coupling reactions of alkyl bromides and iodides, the first Hiyama reactions of (activated) alkyl chlorides have been achieved. In combination with an earlier study of nickel/amino alcohol catalyzed Suzuki couplings, this investigation suggests that the readily available amino alcohols may prove to be useful ligands for a wide range of cross-coupling reactions of alkyl electrophiles. Efforts to substantiate this hypothesis, as well as to exploit enantiopure amino alcohols to accomplish asymmetric processes, are underway.

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Keywords: amino alcohols · cross-coupling · homogeneous catalysis · nickel · silicon

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[2] D. A. Powell, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 7788 – 7789; See also: J.-Y. Lee, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 5616 – 5617.

[3] For reviews of metal-catalyzed cross-coupling reactions, see: a) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, New York, **2004**; b) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-i. Negishi), Wiley Interscience, New York, **2002**.

[4] For recent reviews of cross-coupling reactions of alkyl electrophiles, see: a) A. C. Frisch, M. Beller, *Angew. Chem.* **2005**, *117*, 680 – 695; *Angew. Chem. Int. Ed.* **2005**, *44*, 674 – 688; b) M. R. Netherton, G. C. Fu, *Topics in Organometallic Chemistry: Palladium in Organic Synthesis* (Ed.: J. Tsuji), Springer, New York, **2005**; c) M. R. Netherton, G. C. Fu, *Adv. Synth. Catal.* **2004**, *346*, 1525 – 1532.

[5] For reviews of chiral bipyridine and phenanthroline ligands, see: a) G. Chelucci, R. P. Thummel, *Chem. Rev.* **2002**, *102*, 3129 – 3170; b) A. V. Malkov, P. Kocovsky, *Curr. Org. Chem.* **2003**, *7*, 1737 – 1757; c) N. C. Fletcher, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1831 – 1842; d) E. Schoffers, *Eur. J. Org. Chem.* **2003**, 1145 – 1152.

[6] F. González-Bobes, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 5360 – 5361.

[7] a) In the absence of $NiCl_2$·glyme or of norephedrine, no cross-coupling was observed; b) the Hiyama reaction proceeded best at high concentrations (0.5 M); c) under these conditions, neither $PhSiCl_3$ nor $PhSi(OMe)_3$ proved to be an effective coupling partner; d) the cross-coupling reaction did occur in the absence of 8% H_2O, but less efficiently; the origin of this water (or hydroxide) effect is not yet clear.

[8] Bathophenanthroline proved to be ineffective (< 5% yield).

[9] a) In preliminary experiments under our standard conditions, Hiyama cross-coupling reactions of hindered unactivated secondary bromides, unactivated secondary chlorides, and primary halides have not been efficient (< 50% yield). We have not yet explored the capacity of other nickel/amino alcohol catalysts to achieve Hiyama reactions of these families of substrates; b) we can efficiently cross-couple an unactivated secondary alkyl bromide (> 80% yield) in the presence of an unactivated secondary alkyl chloride (< 2% yield).

[10] a) We have established that gram-scale Hiyama cross-coupling reactions proceed in good yield (ethyl 2-chloropropionate with $PhSiF_3$, 1.44 g (81%)); b) we could effect the selective cross-coupling reaction ($k_{rel} > 50$) of an activated secondary bromide (ethyl 2-bromoisovalerate) in the presence of an unactivated secondary bromide (cyclohexyl bromide); c) a preliminary study indicates that benzylic halides are not useful cross-coupling partners under our standard conditions.

[11] To the best of our knowledge, no examples of nickel- or palladium-catalyzed cross-coupling reactions of secondary α-halocarbonyl compounds with aryl metal reagents (for example, boron, silicon, tin, and zinc) have been described; couplings of primary α-halocarbonyl compounds appear to be limited to Suzuki reactions; for examples, see: a) M. Sato, N. Miyaura, A. Suzuki, *Chem. Lett.* **1989**, 1405 – 1408; b) L. J. Goossen, *Chem. Commun.* **2001**, 669 – 670; c) X.-x. Liu, M.-z. Deng, *Chem. Commun.* **2002**, 622 – 623; d) T.-Y. Lu, C. Xue, F.-T. Luo, *Tetrahedron Lett.* **2003**, *44*, 1587 – 1590; e) Y.-Z. Duan, M.-Z. Deng, *Tetrahedron Lett.* **2003**, *44*, 3423 – 3426.

