## C-C Coupling

## Vinylation of Aldehydes Using Mn/Cr Alloy and a N<sub>4</sub>-Ligand/Ni<sup>II</sup>-Catalyst

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Abstract: We report an efficient and practical protocol for the Cr/Ni-catalyzed vinylation of aldehydes, based on the use of Mn/Cr alloy (ca. 10% Cr) and TMSCI. No additional Cr salts need to be added. In the presence of NiCl<sub>2</sub> (0.3 mol%) and a bis(ketimino)-2,2'-bipyridine as N<sub>4</sub>-chelating ligand (1 mol%), the vinylations proceed smoothly at room temperature. The presence of catalytic amounts of MeOH and LiOAc as additives was found to further promote the efficiency of the catalytic system, even in the absence of the ligand. Detailed reaction monitoring revealed that LiOAc accelerates the product alcohol silylation, thus increasing the turnover rate.

The Cr/Ni-mediated addition of alkenyl and aryl halides/triflates to aldehydes, the so called Nozaki–Hiyama–Kishi (NHK) reaction discovered in 1986,<sup>[1]</sup> is a versatile C–C bond-forming reaction that proceeds under mild conditions (Scheme 1). It features excellent chemoselectivity towards aldehydes and compatibility with a large variety of functionalities.<sup>[2]</sup> However, the



Scheme 1. Stoichiometric and catalytic NHK reactions, and the proposed mechanisms.

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original NHK procedure has serious drawbacks, such as the requirement for larger than stoichiometric amounts of toxic  $Cr^{II}$  salts (usually in the range of 400–1600 mol%), although it is catalytic in nickel.

A catalytic version of the NHK reaction, using about 15 mol% of CrCl<sub>2</sub> (and ca. 3 mol% of NiCl<sub>2</sub>), was reported by Fürstner et al. in 1996 (Scheme 1).<sup>[3]</sup> The salient features are the use of nontoxic, commercial Mn powder as the stoichiometric reductant for recycling Cr<sup>III</sup> to the active Cr<sup>II</sup> species, and trimethylsilyl chloride (TMSCI) as the dissociating agent for the intermediate chromium(III) alkoxides.<sup>[4]</sup> Notably, the regeneration of Cr<sup>II</sup> by reduction of Cr<sup>III</sup> with AI,<sup>[5]</sup> by electro-reduction,<sup>[6]</sup> and by the organic reductant tetrakis(dimethylamino)ethylene (TDAE)<sup>[7]</sup> was also reported by others. The use of [Cp<sub>2</sub>ZrCl<sub>2</sub>] as an effective dissociating agent instead of TMSCI was later developed by Kishi et al.<sup>[8]</sup> With appropriate ligands, a reduction of catalyst loading from typically 10-20 mol% Cr and 1-5 mol% Ni to 1-2 mol% Ni/Cr catalysts was achieved with acceptable rates.<sup>[9]</sup> However, the rather high cost of [Cp<sub>2</sub>ZrCl<sub>2</sub>] is prohibitive for larger scale syntheses and industrial applications. To date, only two types of chiral ligands, that is, endo,endo-2,5-diaminonorbornane (DIANANE)-salens<sup>[10]</sup> and oxazoline/ sulfonamides,<sup>[8a, 11]</sup> have successfully been applied to the asymmetric Cr/Ni-catalyzed vinylation of aldehydes, generating enantiomerically enriched chiral allylic alcohols. In practice, the methods available still suffer from limited substrate scope, low predictability of rates and enantioselectivity, high catalyst loadings, and relatively complex, difficult to access ligand structures.

As a part of our ongoing efforts to improve the efficiency of this catalytic process, we recently reported our investigations of the catalytic roles of nickel and chromium, by using electrochemistry and spectroscopic (UV/Vis) methods.<sup>[12]</sup> In short, we could confirm that a low-valent Ni species (Ni<sup>1</sup> or Ni<sup>0</sup>) is necessary for vinyl halide cleavage, generating an unstable Ni–vinyl species that is prone to rapid decomposition. Importantly, this Ni–vinyl species is stabilized in the presence of Cr, potentially by formation of a bimetallic complex. Furthermore, the generation of low-valent Ni occurs at significantly higher (i.e., milder) potential when Cr is present, and the type of ligand present in the Cr complex affects the efficiency of the Ni<sup>II</sup> reduction. This last result points to an additional catalytic role of Cr when external chemical reductants are used.

Considering Fürstner's catalytic system (Mn/TMSCI/cat.  $CrCI_2$ -Ni $CI_2$ ),<sup>[3]</sup> several limiting factors for the coupling of alkenyl and aryl halides (triflates) with aldehydes need to be mentioned.

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- 1) As for the stoichiometric process,<sup>[13]</sup> two equivalents of vinyl halide are required for satisfactory product yields, as nickel-catalyzed dimerization of the vinyl halides to form dienes was frequently observed.
- 2) The stoichiometric process proceeds smoothly in DMF or DMSO at room temperature, whereas the catalytic process requires 50  $^\circ\text{C}$  in DME/DMF (20:3), as it is too slow at lower temperatures.
- 3) At least 15 mol% of CrCl<sub>2</sub> is required for efficient conversion. At lower catalyst loadings, the coupling proceeds only to a certain degree, but not to completion.
- 4) Anhydrous CrCl<sub>2</sub> is rather expensive, hygroscopic, and is oxidized rapidly in air, resulting in green Cr<sup>III</sup>. The CrCl₂ used should be colorless; pale-green batches notoriously give lower yields. If the reaction indeed proceeded with an efficient  $Cr^{II} \leftrightarrow Cr^{III}$  regeneration process, one would expect the catalysis to proceed regardless of the oxidation state of the chromium source.[14]
- 5) The total turnover is limited by the silylation step. If the silylation is incomplete, the product is obtained as a mixture of allyl alcohol and its silyl ether.

Based on the above-mentioned considerations, we sought to employ bimetallic Mn/Cr alloy instead of the "classical" combination of monometallic Mn powder and Cr salt. We expected the Mn/Cr alloy to act as a single electrochemical entity, thus avoiding the uncertainties of electron transfer to Cr in heterogenous mixtures. In this communication, we report the development of an efficient and practical catalytic vinylation process, based on bimetallic Mn/Cr alloy and a catalytic amount of N<sub>4</sub>-tetradentate ligand/NiCl<sub>2</sub>, operating at very low catalyst loading.

Our investigation started by monitoring the coupling of 1 a and 2a in the presence of NiCl<sub>2</sub>·glyme (0.3 mol%) and ligand (1 mol%) using bimetallic Mn<sub>89</sub>Cr<sub>11</sub> alloy<sup>[15]</sup> (1.5 equiv, that is, 1.3 equiv Mn and 17 mol% Cr) as the stoichiometric reductant and TMSCI as the dissociating agent in anhydrous DMF at ambient temperature for 16 h (Table 1). The yield of the alcohol 3 aa was determined after desilylation. To this end, we devised a method for TMS-deprotection that allowed the whole process to be performed as a one-pot transformation, simply by treatment of the reaction mixture with silica-supported sulfuric acid (H<sub>2</sub>SO<sub>4</sub>·SiO<sub>2</sub>).<sup>[16]</sup> For aliphatic aldehydes as substrates, some silyl enol ether is typically formed as side product. Our desilylation protocol also converts this silvl enol ether back to the corresponding aldehyde. The conversion can be determined reliably without desilylation after stirring of the crude sample with florisil in ethyl acetate.

In the absence of ligand, the reaction proceeded to 29% conversion after 16 h, providing the allylic alcohol 3aa in 16% yield (Table 1, entry 1). Note that the undesired homocoupling of 2a was not observed. For the ligand screening, we focused on N<sub>4</sub>-chelating ligands, as there appears to be no report on the use of such N<sub>4</sub>-tetradentate ligands in coupling reactions of this type. Among the ligands tested, the bis(imino)bipyridine L1<sup>[17]</sup> provided promising results (Table 1, entry 2). Note that the use of the related ligands L2-L4 gave coupling yields



Table 1. Effect of ligands and additives on the coupling reaction of 1 a

1. Reductant, NiCl2•glyme (0.3 mol%),

2. H<sub>2</sub>SO<sub>4</sub>•SiO<sub>2</sub> RT 30 min

nBu L (1 mol%), TMSCI (2 equiv), DMF, RT 16h

and 2 a.<sup>[a</sup>

сно

ommunication

ОН

*n*Bu

L4

DMF (0.26 mL). [b] Determined by GC using biphenyl as the internal standard. [c] In the absence of NiCl<sub>2</sub>·glyme. [d] CrCl<sub>3</sub>·3THF (15 mol%) was used. [e] A trace of homocoupling of 2 a was observed.

that were even lower than in the absence of ligand (Table 1, entries 3-5 vs. 1). This is noteworthy, as 4,4'-di-tert-butyl-2,2'-bipyridine (L4) was reported by Kishi et al. to afford Cr<sup>III</sup> and Ni<sup>II</sup> catalysts effective in the coupling of vinyl halides and aldehydes.[11c]

We next performed extensive screening of additives in the presence of L1 (1 mol%) as ligand and intriguingly found that both MeOH (2 mol%) and LiOAc (0.5 equiv) in DMF had a dramatic effect on reactivity,<sup>[18]</sup> affording 3aa in 86% yield with full conversion (Table 1, entries 6 vs. 7 and 8). Changing the solvent from DMF to THF or DME resulted in lower yields of 3 aa (70-76%), still at full aldehyde conversion. Only a trace of product was formed in MeCN.

We could pinpoint that the catalytic effect of MeOH (EtOH is equally effective)<sup>[19]</sup> is due to the in situ generation of HCl, by reaction with TMSCI. When MeOH was replaced by HCl(g)/dioxane (2 mol%), the product 3aa was obtained in identical yield. We suggest that a small quantity of HCl may be required to activate the metal surface, and/or to promote the in situ generation of Ni/Cr-ligand complex. Ni complex formation is of course crucially important: When the reaction was conducted with L1 (1 mol%) and in the absence of NiCl<sub>2</sub>·glyme, only

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a trace of product resulted, along with a large quantity of the aldehyde silyl enol ether (Table 1, entry 9). The replacement of in situ NiCl<sub>2</sub>·glyme/L1 (0.3:1 mol%, Table 1, entry 6)<sup>[20]</sup> by preformed L1·NiCl<sub>2</sub><sup>[17]</sup> or L4·NiCl<sub>2</sub><sup>[9a]</sup> complexes (0.3 mol%, identical reaction conditions) in the presence of LiOAc, afforded **3aa** in 75% (95% conversion) and 47% (72% conversion) yield, respectively.

We observed that about 1.5 equivalents of free TMSCI were required for efficient coupling, and no coupling at all occurred in the absence of TMSCI. It may be argued that in the reaction mixture, LiOAc and TMSCI could generate TMSOAc and LiCl. Examination of the effects of TMSOAc, LiCl, and AcOH as additives in place of LiOAc clearly confirmed the superior beneficial effect of LiOAc (Table 1, entries 10-12). The replacement of Mn<sub>89</sub>Cr<sub>11</sub> by Mn<sub>93</sub>Cr<sub>7</sub> resulted in lower yield of **3 aa** (Table 1, entry 13). Using a physical mixture of pure Mn<sup>0</sup> (1.5 equiv) and Cr<sup>0</sup> (20 mol%) powders did not promote the reaction at all, demonstrating the synergistic effect resulting from atom-scale mixing of the two metals in the bimetallic particles (Table 1, entry 14). In addition, the use of a mixture of Mn<sup>o</sup> and CrCl<sub>3</sub>·3THF (15 mol%) drastically reduced the yield of 3 aa to 24%, along with the pronounced formation of the silyl enol ether of 1a (Table 1, entry15). Note that no coupling product was formed in the absence of Cr (Table 1, entry 16). Remarkably, the addition of MeOH and LiOAc also significantly promoted the coupling reaction even in the absence of ligand (Table 1, compare entries 17 vs 1) and when the ligand L1 was replaced by L3 (Table 1, entries 19 vs 4), the product 3aa was obtained in high yield of 75-80%. In contrast, the quaterpyridine L2 and bipyridine L4 gave only trace amounts of 3aa, even in the presence of additives (Table 1, entries 18 and 20).

To gain further insight into the catalytic effect of LiOAc, we monitored the formation of the coupling products **3aa** and **4aa** as a function of time (Figure 1). For this purpose, aliquots of the reaction mixture were withdrawn, stirred with florisil in EtOAc, filtered, and analyzed by GC. The results are summarized in Figure 1, the conversion of starting aldehyde **1a** and yields of **3aa** and **4aa** are plotted as a function of reaction time.

In the absence of LiOAc (Figure 1 A), the graph clearly shows that in the initial phase of the reaction (up to 9 h, 56% conversion), up to 24% of the alcohol **3aa** (red line) was present in an amount almost equal to its silyl ether **4aa** (green line). Later on, the amount of silyl ether **4aa** increased further, while that of the alcohol **3aa** first decreased and then remained nearly unchanged over the further course of reaction. After 24 h (not shown in graph), a mixture of **3aa** (11%) and **4aa** (45%) was obtained at an aldehyde conversion of 86%. The concentration/time profiles of **3aa/4aa** point to initial liberation of the alcohol product **3aa** from a metal–alkoxide intermediate, and subsequent transformation to its silyl ether **4aa**.

In the presence of 50 mol% LiOAc (Figure 1B), the reaction proceeds significantly faster, and completion is reached within about 12 h. Most importantly, the silyl ether **4aa** was present as the major product over the whole course of the reaction, and increased steadily. In contrast, the amount of free alcohol (**3 aa**, red line) went through a maximum (13%) at about 6 h



Figure 1. Effect of LiOAc on the coupling reaction of 1 a and 2 a, concentration versus time profiles.

and then decreased to a persistent level of approximately 4%. Apparently, the LiOAc additive facilitates the silylation step, potentially by cleavage of chromium–alkoxide intermediates, thus increasing overall reaction rate.

With the newly developed catalytic protocol in hand, we set out to study the substrate scope with regard to various aldehydes and vinyl/aryl iodides/triflate (Table 2).<sup>[21]</sup> The coupling of 2a with the aliphatic aldehydes 1a-c proceeded smoothly under our catalytic conditions, giving the corresponding allylic alcohols in very good isolated yields of 75-85% (Table 2, entries 1–3). With the sterically demanding aldehyde 1 d, a moderate yield of 3da was obtained (Table 2, entry 4). Moderate yields were also obtained with aromatic aldehydes 1e and f (Table 2, entries 5 and 6), For aromatic aldehydes, competing pinacol coupling is a major side reaction. In line with this, electron-poor aromatic aldehyde 1g gave pinacol coupling exclusively (Table 2, entry 7). The reaction of 2b, the triflate analogue of 2a, proceeded better in the absence of LiOAc or LiCl, affording 3aa in 26% at 43% conversion after 24 h (23% yield when no L was added). Gratifyingly, by increasing the amount of NiCl<sub>2</sub> to 2 mol% and in the absence of ligand, 3 aa was obtained in 76% yield with full conversion and only a trace of 2b dimerization was observed (Table 2, entry 8).

The coupling of the aliphatic aldehyde 1a with iodobenzene (**2**c) did not reach completion under standard conditions. However, increasing the amount of LiOAc to 1.0 equivalent significantly speeded up the reaction, and the benzyl alcohols **3** were obtained in yields of 50–80% (Table 2, entries 9–13), together with trace amounts of biphenyl. The reactivity of 1-iodocyclopentene (**2**e) and of the 1-iodohexenes (*E*)-**2**f and (*Z*)-

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Table 2. The coupling reaction of aldehydes 1 and vinyl/aryl iodides/tri-
flate <b>2</b> in the presence of <b>L1</b> , affording the alcohols <b>3</b> . <sup>[a]</sup>

1. Mn <sub>89</sub> Cr <sub>11</sub> , NiCl <sub>2</sub> •glyme, L1 OH								
RCHO + $R^{1}$ -X $\frac{WEOH, EIOAC, TWSOI, DWF, RT}{2, H_{2}SO_{4} SIO_{2} RT}$ R R <sup>1</sup>								
1 2 3								
	2a 2b	2c	20 2d	2e	2f	2g		
	R–CHO	R <sup>1</sup> X	LiOAc	t	3	Yield		
			[equiv]	[h]		[%] <sup>[b]</sup>		
1	1 a (PhCH <sub>2</sub> CH <sub>2</sub> -)	2 a	0.5	15	3 aa	85 (74)		
2	1 b (H <sub>15</sub> C <sub>7</sub> -)	2 a	0.5	15	3 ba	75		
3	1 c ( <i>cy</i> Hex-)	2 a	0.5	15	3 ca	78		
4	<b>1 d</b> ( <i>t</i> Bu-)	2 a	0.5	15	3 da	55		
5	<b>1 e</b> (Ph-)	2 a	0.5	15	3 ea	65		
6	<b>1 f</b> (4-OMe-Ph-)	2 a	0.5	15	3 fa	45		
7	<b>1 g</b> (4-CN-Ph-)	2 a	0.5	15	3 ga	0 <sup>[c]</sup>		
8	1 a (PhCH <sub>2</sub> CH <sub>2</sub> -)	2 b	-	24	3 aa	26 (76 <sup>[d]</sup> )		
9	1 a (PhCH <sub>2</sub> CH <sub>2</sub> -)	2 c	1.0	24	3 ac	80 (74)		
10	1 b (H <sub>15</sub> C <sub>7</sub> -)	2 c	1.0	24	3 bc	70		
11	1 c ( <i>cy</i> Hex-)	2 c	1.0	24	3 cc	65		
12	<b>1 e</b> (Ph-)	2 c	1.0	24	3 ec	50		
13 <sup>[e]</sup>	1 a (PhCH <sub>2</sub> CH <sub>2</sub> -)	2 d	1.0	24	3 ad	52 <sup>[f]</sup> (34)		
14 <sup>[e]</sup>	1 a (PhCH <sub>2</sub> CH <sub>2</sub> -)	2 e	1.0	24	3 ae	56 (51)		
15 <sup>[e]</sup>	1 a (PhCH <sub>2</sub> CH <sub>2</sub> -)	2 f	1.0	24	3 af	50 (35)		
16 <sup>[e]</sup>	1 a (PhCH <sub>2</sub> CH <sub>2</sub> -)	2 g	1.0	24	3 ag	30 (12)		

[a] Reactions were carried out using 1 (2.5 mmol), 2 (1.2 equiv),  $Mn_{89}Cr_{11}$  (1.5 equiv),  $NiCl_2$ ·glyme (0.3 mol%), L1 (1 mol%), MeOH (2 mol%), LiOAc (0.5/1.0 equiv), TMSCI (2.1/2.7 equiv) in DMF (2.2 mL) at room temperature. [b] Isolated yield after column chromatography. In parenthesis, when no ligand was added. [c] Only pinacol coupling product was observed. [d] 2 mol% of NiCl\_2·glyme was used. [e] The reaction did not reach completion, both 1 and 2 remained. [f] 4,4'-Bis(ethoxycarbonyl)diphenyl was obtained in 5% based on 2d.

**2g** in the coupling with **1a** was found to be lower than that of **2a** and **2c**. After 24 h, the coupling products **3ae-ag** were obtained in moderate yield only (Table 2, entries 14–16), with some **1a** and **2** remaining. Extension of the reaction times improved the product yields only slightly. Notably, no *Z/E* isomerization was detected in the reactions of **2f** and **2g** (Table 2, entries 15, 16). Upon increasing NiCl<sub>2</sub> to 0.5 mol% (**L1** 1.5 mol%), however, partial  $Z \rightarrow E$  isomerization was observed with **2g**,<sup>[23]</sup> yielding a 11:1 *Z/E* product mixture in 38% yield at 74% conversion after 18 h.

In summary, we have developed an efficient and practical protocol for the coupling of vinyl/aryl iodides/triflate and aldehydes. The use of the bimetallic Mn/Cr alloy apparently provides lower reduction potential, and no additional Cr catalyst is required. As a consequence, aliphatic aldehydes are particularly suitable substrates, whereas aromatic aldehydes tend to undergo pinacol coupling. High catalytic efficiency is achieved at very low Ni<sup>II</sup>/L1 catalyst loading, in the presence of MeOH and LiOAc as additives. The reaction also proceeded well in the absence of ligand or with commercially available tetraphenylporphyrin (L3), albeit with slightly lower yield. This protocol can be considered as an alternative for large scale applications. To the best of our knowledge, we report here the first case of using a task-specific alloy in catalytic organometallic synthesis. Further mechanistic studies, for example, on the question of surface versus homogeneous reaction, are underway.

### **Experimental Section**

General procedure:<sup>[23]</sup> A solution of NiCl<sub>2</sub>·glyme in DMF (0.19 mL, 0.04  $\mu$  (freshly prepared), 7.5  $\mu$ mol, 0.003 equiv) and MeOH (2.0  $\mu$ L, 50  $\mu$ mol, 0.02 equiv) was added to a suspension of Mn<sub>89</sub>Cr<sub>11</sub> powder (205 mg, 3.75 mmol, 1.50 equiv), L1.0.5 THF (15.0 mg, 25 µmol, 0.01 equiv), and LiOAc (0.5/1.0 equiv) in dry DMF (2.0 mL) under an argon atmosphere (note that the reaction is air sensitive). The mixture was stirred for 15 min, followed by the addition of TMSCI (2.1/2.7 equiv). After stirring for 5 min, resulting in a very dark brown mixture, 2 (1.2 equiv) and aldehyde 1 (2.5 mmol, 1.0 equiv) were added successively. The reaction mixture was stirred at ambient temperature for 15/24 h under Ar. The resulting very dark brown mixture was then diluted with EtOAc (2 mL). H<sub>2</sub>SO<sub>4</sub>·SiO<sub>2</sub> (ca. 250–300 mg) was added and the mixture was stirred for about 30 min for TMS deprotection. After completion (by TLC), silica gel (ca. 0.5 g) and EtOAc (20 mL) were added and the mixture was stirred vigorously for 30 min. This should result in a green powder in solution (if not, use spatula to delump and stir longer). The resulting mixture was subjected to suction filtration (washing with EtOAc). After concentration of the filtrate in vacuo, the residue was purified by column chromatography on silica gel (EtOAc/cyclohexane) to give the alcohol 3.

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- [17] It has been reported that L1 acts as a tetradentate ligand, preferentially forming six-coordinate Ni<sup>II</sup> complexes, see: G. A. Griffith, M. J. Al-Khatib, K. Patel, K. Singh, G. A. Solan, *Dalton Trans.* 2009, 185–196.

- [18] 1 to 5 mol% MeOH gave similar results. Other additives tested included NaOAc, NaOBz (Bz=benzoyl), LiOBz, Lil, LiCl, and were found to be less effective. The use of Et<sub>3</sub>N·HCl and LiCl as additives was found to promote the Cr<sup>II</sup>/Ni<sup>II</sup>-mediated coupling reaction, see ref. [11a].
- [19] The activating effect of alcohol was first observed by using a highly effective batch of L1, which turned out to be contaminated with a small amount of EtOH. As we could not prepared an absolutely solvent-free ligand, L1-0.5 THF was prepared and used in our study.
- [20] The optimal NiCl<sub>2</sub>/L ratio was found to be 1:3, a lower amount of ligand resulted in lower conversion and lower product yield.
- [21] Independent of the vinyl halide used, the silyl enol ethers of enolizable aldehydes were observed as byproducts in all cases. When the product allylic alcohols **3** are isolated as their silyl ethers **4**, potential contamination by the silyl enol ether of aldehyde has to be kept in mind, as the chromatographic behavior of the product silyl ethers and aldehyde silyl enol ethers are typically similar. In practice, the pure allylic alcohol product is best isolated after desilylation.
- [22] Generally, the extent of  $Z \rightarrow E$  isomerization can be suppressed by lowering the Ni/Cr ratio, as demonstrated by Kishi et al., in the course of an extensive study on geometrical isomerization effected by Ni catalysts during the Cr/Ni-mediated coupling, although no yields were given, see reference [11f].
- [23] The Mn/Cr powder was slowly dissolved during the reaction progress and only a trace of metal powder remained upon completion. Effective stirring (ca. 750 1 min, oval shaped stir bar) of the reaction mixture is essential for promoting the coupling.

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# COMMUNICATION

## C-C Coupling

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□ Vinylation of Aldehydes Using Mn/Cr Alloy and a N₄-Ligand/Ni<sup>II</sup>-Catalyst



### Fantastic four—Mn/Cr-alloy + Ni/N<sub>4</sub>:

When a Mn/Cr alloy (ca. 10% Cr) is used as the stoichiometric reductant, the catalytic vinylation of aldehydes proceeds efficiently in the presence of a Ni catalyst (see scheme: 0.3 mol% Ni<sup>II</sup>, w/wo 1 mol% of N<sub>4</sub>-ligand). No additional Cr catalyst is required. There is no wasteful homocoupling of vinyl iodides to dienes, and the product allylic alcohol is isolated without aqueous workup.

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