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## Carbon-carbon bond formation in neutral aqueous medium by modification of the Nozaki-Hiyama reaction

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Abstract—A carbon–carbon bond forming reaction has been developed by modifying the Nozaki–Hiyama reaction using a chromium(II)-aminopolycarboxylate complexes in a neutral aqueous medium at room temperature. Aldehydes and ketones can be coupled with aralkyl and aryl halides in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

A selective carbon-carbon bond forming reaction was described by Nozaki and Hiyama<sup>1</sup> in 1977 based on the addition of alkenyl, alkynyl, allyl or vinylchromium(III) compounds to aldehydes in a mild anhydrous medium. The use of CrCl<sub>2</sub> in anhydrous DMF resulted in well established reaction conditions.<sup>2</sup> A catalytic amount of NiCl<sub>2</sub> in the reaction mixture increased the chemoselectivity of numerous C-C-bond forming reactions (the Nozaki-Hiyama-Kishi reaction<sup>3,4</sup>). Fürstner<sup>5</sup> proposed a catalytic solution for Cr(II) using reactive Mn powder as the electron source reducing the cost of the reagent and the amount of toxic salts. The detailed evaluation wide-ranging applications of the use of and organochromium(III) reagents for C-C bond formation have been abundantly reviewed.6-9

 $Cr(EDTA)^{2-}$  complex in the so-called biomimetic medium.<sup>15</sup>

In this work we demonstrate that the Nozaki–Hiyama reaction<sup>2</sup> after modification, can be used in a neutral aqueous medium. The selectivity of these reactions can be regulated by added ligands.<sup>10,13,15</sup>

To get the best reaction conditions, benzaldehyde (1) and benzyl bromide (3) were reacted with  $Cr^{II}L$  complexes (L=acetate (OAc); imino-diacetate (IDA); nitrilo-triacetate (NTA); ethylenediaminetetra-acetate (EDTA) in neutral aqueous/DMF solution at room temperature. 1,2-Diphenylethanol (7) as well as the by-products, toluene (11), benzyl alcohol (12), 1,2-

 $\begin{array}{c} O \\ Ph \\ R^{1} \\ R^{1} \\ R^{1} \\ R^{2} \\ R^{1} \\ R^{2} \\ R^{2} \\ R^{2} \\ R^{1} \\ R^{1}$ 

Our recent results have shown, that Cr(II)-based synthetic chemistry can be transferred to a neutral aqueous medium<sup>10,11</sup> and that the chemo<sup>12</sup> as well as the enantioselectivity<sup>13,14</sup> can be regulated carefully by added ligands. Intramolecular carbon–carbon bond formation was executed on the morphine skeleton using a diphenylethane (13) and 1,2-diphenyl-1,2-ethanediol (14) were detected in the crude product mixtures (see Table 1).

In a typical experiment, Na<sub>2</sub>EDTA·2H<sub>2</sub>O (4.66 g, 12.5 mmol) was dissolved in 7.2 cm<sup>3</sup> aqueous 2.78 M KOH solution (40 mmol OH<sup>-</sup>) and 7.8 cm<sup>3</sup> water at room temperature in a three-necked flask using standard Schlenk-techniques. DMF (15 cm<sup>3</sup>) was then added and the magnetically stirred solution was deoxygenated by bubbling with argon for 15 min. Then [Cr(OAc)<sub>2</sub>·H<sub>2</sub>O]<sub>2</sub>

*Keywords*: Nozaki–Hiyama reaction; chromium(II) complex; carbon–carbon bond; organochromium(III) complexes.

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Table 1. Reaction of benzaldehyde and benzyl bromide with Cr<sup>II</sup>L complexes

Entry	1 (mmol)	3 (mmol)	Ligand	Cr <sup>II</sup> L (mmol)	pH	Method	⁰∕₀a,b,e,f			
							7	1	12	14
1	5	10	OAc	20	5.5	$Cr^{II}L + (1+3)^{c}$	_	69	31	_
2	5	10	IDA	20	6.5	$Cr^{II}L + (1+3)^{c}$	8	49	43	_
3	5	10	NTA	20	6.5	$Cr^{II}L + (1+3)^{c}$	26	22	49	3
4	5	10	EDTA	20	6.0	$Cr^{II}L + (1+3)^{c}$	32	19	25	24
5	5	10	EDTA	20	6.0	$Cr^{II}L + 1 + 3^d$	6	10	50	34
6	5	10	EDTA	20	6.0	$Cr^{II}L + 3 + 1^{d}$	5	19	61	15
7	5	10	EDTA	20	6.0	$(1+3) + Cr^{II}L$	87	_	8	5
8	5	5	EDTA	10	6.0	$(1+3)+Cr^{II}L$	89	_	6	5

<sup>a</sup> Calculated from the <sup>1</sup>H NMR spectra and HPLC chromatograms.

<sup>b</sup> Calculated for 1.

<sup>c</sup> Mixture of **1** and **3** was added dropwise within 10 min as suggested by Nozaki and Hiyama.

<sup>d</sup> First 1 or 3 was added to Cr<sup>II</sup>L in one portion and after 60 seconds 1 or 3 in one portion.

e 13<5%.

f 11 not measured (can be calculated from the mass balance).

(1.88 g, 10 mmol Cr(II)) was added in one portion under argon, and the color of the solution immediately turned blue indicating the formation of the reactive complex<sup> $\dagger$ </sup> [Cr<sup>II</sup>(EDTA)]<sup>2-</sup>. The pH of the solution was 6.0 (checked by pH-potentiometry) and the solution was poured into a dropping funnel under argon. In another three-necked flask, 10 cm<sup>3</sup> water and 10 cm<sup>3</sup> DMF was deoxygenated with argon and then 0.53 g (5 mmol) benzaldehyde and 0.86 g (5 mmol) benzyl bromide were added into the solvent mixture. The [Cr<sup>II</sup>(EDTA)]<sup>2-</sup> solution was added dropwise to the benzaldehyde-benzyl bromide mixture under argon within 60 min. The color of the reaction mixture changed slowly to dark violet. The reaction vessel was than stoppered under a slight overpressure of argon, and stirring was continued for 6 h.<sup>‡</sup>

Using  $Cr(OAc)_2$  as reductant (entry 1) unchanged starting aldehyde (1) and side products (11, 12, 13) were found in the crude mixture. Modifying the coordination sphere of the Cr(II) reagent by adding ligands to give the Cr(IDA), Cr(NTA)<sup>-</sup> and Cr(EDTA)<sup>2-</sup> complexes, gave the coupled product (7) in low-moderate quantities (entries 2–4). The formation of (7) fell when the substrates were added separately (entries 5, 6). The highest conversion of (7) was reached when the  $Cr(EDTA)^{2-}$  complex was added slowly to the mixture of (1) and (3) (entry 7). The 1:2:4 carbonyl:halide:Cr(II) ratio suggested by Nozaki and Hiyama (entries 1–7) could be decreased to 1:1:2 under then reaction conditions (entry 8).

Using the optimal reaction conditions further carbon-carbon bond formation reactions can be realized with good or moderate yields (Table 2). Acetophenone (2) as well as the less reactive chlorides (4, 6) can also be coupled as a result of the increased reactivity provided by the EDTA ligand.

Our results open new possibilities in the development of the classical Nozaki–Hiyama reaction. The neutral aqueous medium seems to be ideal for application in various natural product synthesis. The selectivity controlled by the complex reagents may allow chiral ligands to lead to the enantioselective reactions. This work is in progress in our laboratory.

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**Table 2.** Coupling reactions with the  $Cr(EDTA)^{2-}$  complex

Entry		Substrate	Product	Yield (%) <sup>a</sup>
1	1	3	7	78
2	1	4	7	72
3	1	5	9	70
4	1	6	9	66
5	2	3	8	68
5	2	4	8	64
7	2	5	10	61
3	2	6	10	59

<sup>a</sup> Isolated yields calculated for the carbonyl compounds.

<sup>&</sup>lt;sup>†</sup> For the preparation of the Cr<sup>II</sup>L complexes solution equilibrium calculations<sup>16</sup> using the known formation constants<sup>17</sup> gave the desired pH.

<sup>&</sup>lt;sup>‡</sup> The mixture was extracted with ether (5×), the ethereal phase was washed with water (3×), than dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under diminished pressure. The analyses were also controlled by isolating (**3**). The main product was separated using column chromatography, (Kieselgel 60, hexane/acetone (6:1)) and was identified by <sup>1</sup>H and <sup>13</sup>C NMR (Bruker AM 360) spectra. The isolated products had all characteristics identical with that of an authentic sample. The raw mixtures were analysed by HPLC performed on a Chiralcel OJ (250×4.6 mm) column equipped with a BST-silica precolumn (40×4.6 mm). The column was attached to a Jasco PU-980 solvent delivery system and pressure moderator. Peaks were monitored by UV detection using a Jasco MD-910 diode array detector. Solvent mixture hexene/2-propanol 95:5 (v/v) was used, the flow rate was 0.8 cm<sup>3</sup> min<sup>-1</sup>.

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