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Generation of chromioenamines by reduction of *O*-acetyloximes with chromium(II) and their application†

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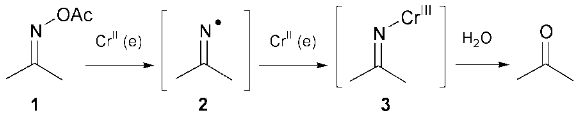
Chromioenamines can be generated by treatment of *O*-acetyloximes with chromium(II) *via* two steps of one-electron reduction and successive isomerization, and the species react with aldehydes to give γ-amino alcohols after reduction with $LiAlH_4$.

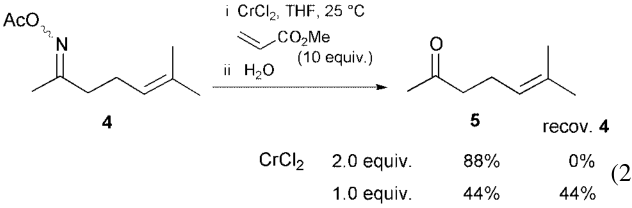
Treatment of *O*-acetyloximes **1** with low valent metals such as Cr(II) and Ti(III) under aqueous conditions is a mild deoximation procedure.[1] The process includes the reductive cleavage of N–O bonds leading to *N*-metal imines **3**[2] *via* iminyl radicals **2**,[3] and the hydrolysis of the formed imines to obtain ketones [eqn. (1)].



(1)

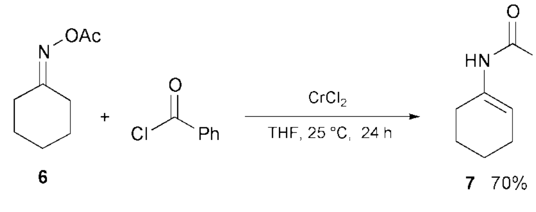
In order to examine the utilization of the formed reactive species **2** or **3** for carbon–carbon formation, we conducted the chromium(II)-mediated deoximation in aprotic solvents.[4]

The *O*-acetyloxime **4** was treated with 2 equiv. of chromium(II) chloride in the presence of 10 equiv. of methyl acrylate to give the corresponding deoximated ketone **5** in 88% yield after hydrolysis [eqn. (2)]. Nitrogen-containing five-membered ring compounds derived *via* intramolecular radical cyclization were not observed,[3] and no coupling product between **4** and the acrylate was obtained. When the amount of chromium(II) chloride was reduced to 1 equiv. of the oxime **4**, the ketone **5** was obtained in 44% yield and **4** was recovered in 44% yield. These results suggest that the second one-electron reduction of the iminyl radical **2** to the *N*-chromium imine **3** proceeds faster than the first reduction of **1** to **2**.



(2)

Trapping of the formed *N*-chromium imine **3** was examined. Although the reduction of the cyclohexanone *O*-acetyloxime **6** with $CrCl_2$ in the presence of Me_3SiCl resulted only in deoximation leading to cyclohexanone, the reduction in the presence of the benzoyl chloride gave **7** in 70% yield along with benzamide in 8% yield [eqn. (3)].[1b] The expected *N*-acyl imine derived from *N*-chromium imine **3** was not obtained, and instead a chromioenamine was trapped as **7**.

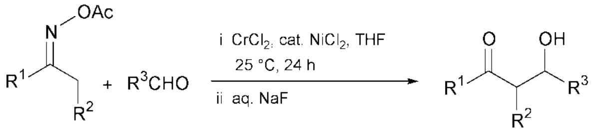


(3)

Thus, carbon–carbon bond formation with this chromioenamine[5] was investigated in the presence of an aldehyde in the aprotic solvent. Treatment of a mixture of acetone *O*-acetyloxime (**8**, 2 equiv.) and benzaldehyde with $CrCl_2$ (8 equiv.) in THF at 25 °C for 24 h followed by hydrolysis with water gave 4-phenyl-4-hydroxybutan-2-one (**9**) in 23% yield. The quenching procedure affected the yields considerably, probably due to the strong chelation of the adducts to chromium(III). The yield was improved to 88% by quenching with aqueous NaF solution (Table 1 run 2).[6–8] Although the reaction proceeded more slowly in the case of aliphatic aldehydes, addition of a catalytic amount of $NiCl_2$ accelerated the reaction rate and improved the yields.[9]

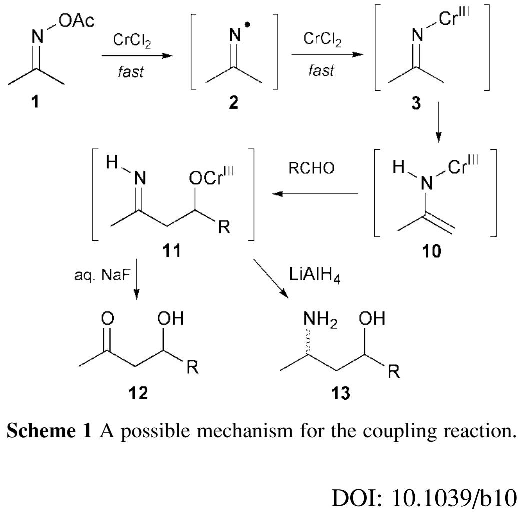
A possible mechanism is shown in Scheme 1. One electron reduction of an *O*-acetyloxime with chromium(II) gives the

Table 1 Aldol reactions between *O*-acetyloximes and aldehydes with chromium(II)[a]



Run	R^1	R^2	R^3	Yield (%)[b]	*syn–anti*[c]
1	Me	H (**8**)	Ph	84[d] (**9**)	—
2	**8**		Ph	88[e]	—
3	**8**		n-C_8H_{17}	67	—
4	**8**		c-C_6H_{11}	74	—
5	-$(CH_2)_4$-(**6**)		Ph	81[ef]	36:64
6	**6**		$Ph(CH_2)_2$	54[e]	6:94

[a] Reaction conditions as in typical procedure (ESI) unless otherwise stated. [b] Isolated yields. [c] Isomer ratios were determined by isolation and/or NMR. [d] The reaction was completed in 8 h. [e] The reaction was conducted without addition of $NiCl_2$. [f] 8 mol of $CrCl_2$ was used per mol of benzaldehyde.



Scheme 1 A possible mechanism for the coupling reaction.

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† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b1/b105357b/

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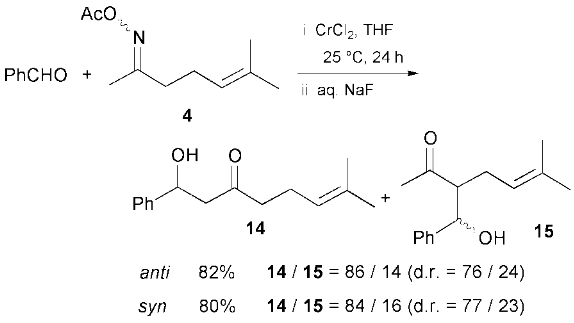
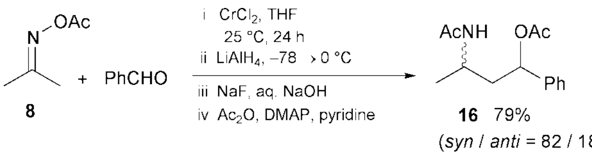
imine radical **2**,[3] which is then subjected to the second one electron reduction to give **3**. The imine **3** is isomerized to chromioenamine **10**,[1d,10] and the chromioenamine reacts with an aldehyde to give **11**.[11] Hydrolysis of **11** gives the aldol adduct **12**. Metalloenamines are usually prepared by deprotonation of imine derivatives with strong bases,[5] however, the procedure does not require such bases. Attempts to reduce the amount of chromium(II) with manganese and Me_3SiCl resulted in deoximation probably due to the fast trapping of the chromium imine **3** or the chromioenamine **10** with Me_3SiCl.[12]

When *anti*- and *syn*-**4** were employed in the reaction, almost the same product distributions were observed [eqn. (4)]. The major product was an aldol adduct **14** at the less hindered carbon. This result supports the proposed Scheme 1, in which the two reactions involve the same iminyl radical as the intermediate.



(4)

In order to utilize the nitrogen-containing adduct **11**, reduction of **11** leading to a γ-amino alcohol **13** was examined.[13] A mixture obtained from **8** and benzaldehyde was treated with $LiAlH_4$ (10 equiv.) at −78 °C, and the temperature of the mixture was gradually raised to 0 °C. Quenching of the mixture with alkaline NaF solution followed by acetylation gave the acetylated γ-amino alcohol **16** in 79% yield [eqn. (5)].[14,15] The yield was increased by addition of a catalytic amount of $NiCl_2$. The results of the preparation of γ-amino alcohols from *O*-acetyloximes and aldehydes with $CrCl_2$ and $NiCl_2$ are summarized in Table 2.



(5)

In conclusion, chromioenamines are generated by treatment of *O*-acetyloximes with chromium(II) *via* sequential reduction and isomerization. These react with aldehydes to obtain γ-amino alcohols after reduction with $LiAlH_4$. The reaction proceeds under mild conditions and does not require strong bases such as LDA.

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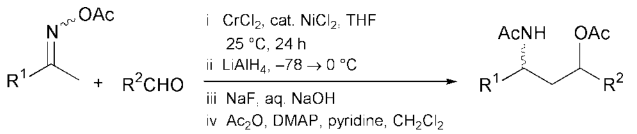
Table 2 Preparation of γ-amino alcohols from *O*-acetyloximes and aldehydes[a]



Run	R^1	R^2	Yield (%)[b]	*syn–anti*[c]
1	Me (**8**)	Ph	86 (**16**)	70:30
2	**8**	Ph	79[d]	82:18
3	**8**	$Ph(CH_2)_2$	65	69:31
4	**8**	c-C_6H_{11}	71	69:31
5	Ph (**17**)	Ph	88	42:58
6	**17**	$Ph(CH_2)_2$	70	53:47
7	**17**	c-C_6H_{11}	71	54:46

[a] Reaction conditions as in typical procedure (ESI) unless otherwise stated. [b] Isolated yields. [c] Isomer ratios were determined by isolation and/or NMR. [d] The reaction was conducted without addition of $NiCl_2$.

Notes and references

1 (*a*) Cr: E. J. Corey and J. E. Richman, *J. Am. Chem. Soc.*, 1970, **92**, 5276; (*b*) R. B. Boar, J. F. McGhie, M. Robinson, D. H. R. Barton, D. Horwell and R. V. Stick, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1237; (*c*) Ti: G. H. Timms and E. Wildsmith, *Tetrahedron Lett.*, 1971, 195; (*d*) D. H. R. Barton and S. Z. Zard, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2191.

2 H. Tsutsui and K. Narasaka, *Chem. Lett.*, 1999, 45.

3 Ni: J. Boivin, A.-M. Schiano, S. Z. Zard and H. Zhang, *Tetrahedron Lett.*, 1999, **40**, 4531; J. Boivin, E. Fouquet and S. Z. Zard, *Tetrahedron Lett.*, 1990, **31**, 3545.

4 We thank Mr Shigeki Nakatsukasa of Kyoto University for conducting an initial investigation of chromioenamines.

5 For metalloenamines, see: S. F. Martin, *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 2, ch. 1.16, p. 475.

6 The yield was improved to 92% when the mixture was quenched with aq. NaF solution for 48 h.

7 Among the oxime derivatives examined, *O*-acetyl gave the best result. Results with the other oxime derivatives are as follows: *O*-benzoyloxime, 58%; *O*-mesyloxime, 75%; *O*-tosyloxime, 47%; *O*-trimethylsilyloxime, 12%.

8 Although the amounts of *O*-acetyloxime and chromium(II) chloride can be reduced to 1.2 and 3.6 equiv., respectively, without affecting the yield, the couplings required longer reaction times.

9 (*a*) K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto and H. Nozaki, *J. Am. Chem. Soc.*, 1986, **108**, 6048; (*b*) S. Py, C. W. Harwig, S. Banerjee, D. L. Brown and A. G. Fallis, *Tetrahedron Lett.*, 1998, **39**, 6139.

10 (*a*) J. V. Braun and W. Rudolph, *Ber.*, 1934, **67B**, 269; (*b*) For reverse isomerization, see: K. A. Miller, T. W. Watson, J. E. Bender IV, M. M. Banaszak-Hall and J. F. Kampf, *J. Am. Chem. Soc.*, 2001, **123**, 982.

11 J.-E. Dubois, G. Axiotis and E. Bertounesque, *Tetrahedron Lett.*, 1985, **26**, 4371; L. Wessjohann and T. Gabriel, *J. Org. Chem.*, 1997, **62**, 3772.

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13 K. Narasaka, Y. Ukaji and S. Yamazaki, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 525.

14 Because chromium(III) salts can be reduced with $LiAlH_4$, an excess amount of the hydride source was required to complete the reduction. See: Y. Okude, S. Hirano, T. Hiyama and H. Nozaki, *J. Am. Chem. Soc.*, 1977, **99**, 3179.

15 The following reducing agents were examined: i-Bu_2AlH (51% yield, *syn–anti* = 72:28), $Na(MeOCH_2CH_2O)_3AlH$ (10%, 33:67); $LiEt_3BH$ (10%, 68:32), Li(*sec*-Bu)$_3$BH (35%, 63:37).