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Chromium-catalyzed olefination of arylaldehydes with haloforms assisted by 2,3,5,6-tetramethyl-*N,N'*-bis(trimethylsilyl)-1,4-dihydropyrazine

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Chromium-catalyzed olefination of arylaldehydes with haloforms was achieved using 2,3,5,6-tetramethyl-*N,N'*-bis(trimethylsilyl)-1,4-dihydropyrazine (1a) as an organic reducing agent, giving *β*-halostyrene derivatives in a *trans*-selective manner. The reaction required no metal powders, such as zinc and manganese, as reductants, thereby minimizing metal-based reaction waste.

Olefins are an important carbon-carbon linkage in organic molecules due to their significance in π-conjugated organic materials and synthetic utilities for installing various functional groups across the C=C bonds. Typically, elimination reactions of alcohols and alkyl halides are applied for C=C bond formation, but the site- and stereoselectivities of the new C=C bonds are problematic due to the requirement of harsh reaction conditions for the elimination step. Carbonyl olefination has been developed as a reliable method to construct new C=C bonds at a specific position within the organic skeletons. Leading examples for carbonyl olefination are the use of phosphorous and sulfur-based reagents, i.e. Wittig olefination and Julia olefination.[1] Further elaboration on the development of carbonyl olefination reactions is significant for using not only group 13-16 element compounds[2] but also transition metal species, the latter of which contain metal carbenoids and metal carbenes as key intermediates in the olefination reaction.[3,4] Remarkable progress has been made in this area toward utilizing simple organic compounds as sources of olefination agents in combination with low-valent transition metal species: for example, Takai and Utimoto as well as Takeda independently demonstrated that $TiCl_4$/Zn and $Cp_2Ti[P(OEt)_3]_2$ promoted olefination of aldehydes and ketones with geminal dihalides and dithioacetals as olefination sources, respectively (Fig 1(a)).[5] Takai *et al.* further explored carbonyl olefination with wide functional group tolerance using chromium(II) dihalide. In fact, excess amounts of $CrCl_2$-mediated olefination of carbonyl compounds with geminal dihalides,[6] while the catalytic variant was demonstrated using CHI_3, Me_3SiCHX_2 (X = Br, I), and (pin)$BCHCl_2$ in combination with excess amounts of metal reductants, such as zinc or manganese powders (Fig 1(b));[7] however, more than stoichiometric amounts of metal salt waste were always co-produced in the previously developed low-valent early transition metal-mediated and -catalyzed olefination reactions.

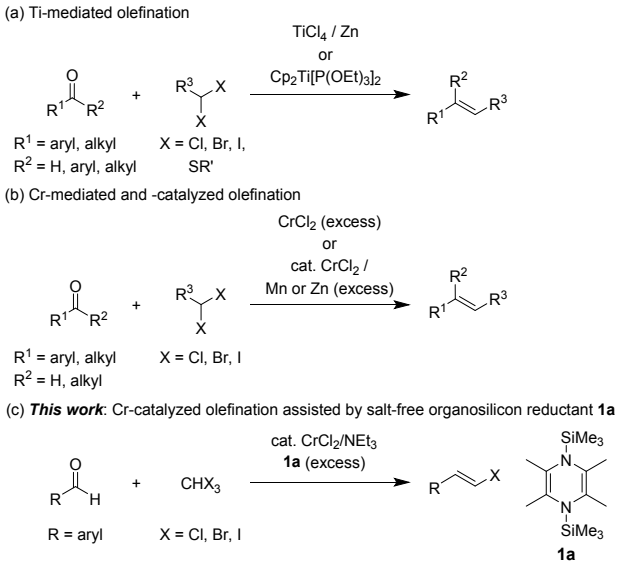

Fig. 1 Carbonyl olefination by transition metal complexes.

Recently, we found Cr-catalyzed cyclopropanation of alkenes with $CHBr_3$ in the presence of an organosilicon reductant, 2,3,5,6-tetramethyl-*N,N'*-bis(trimethylsilyl)-1,4-dihydropyrazine (**1a**),[8] giving bromocyclopropanes *via in situ*-generation of chromium bromocarbene intermediates,[9,10] in which the superior reducing ability of **1a** was key to the high catalytic activity. Such superior reactivity of the chromium bromocarbene species led us to further investigate their application in organic synthesis. Herein, we report chromium-catalyzed olefination of various aldehydes with haloform in the presence of **1a** as a reductant and triethylamine as an additive, giving a series of synthetically useful *trans*-*β*-halostyrene derivatives (Fig 1(c)). This is the first example of the elimination of excess amounts of metal salt waste among early transition metal-catalyzed carbonyl olefination reactions.

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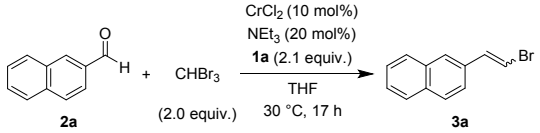
We began by searching for the best reductant upon addition of **1a** (2.1 equiv.) to a mixture of 2-naphthaldehyde (**2a**), $CHBr_3$ (2.0 equiv.), $CrCl_2$ (10 mol%), and NEt_3 (20 mol%) in THF as standard reaction conditions, and the results are summarized in Table 1. Organosilicon compound **1a** served as a reductant for producing the corresponding *trans*-β-bromoalkene **3a** in 74% yield (70% isolated) without contamination of the corresponding β-chloroalkene **3a'**, which was often involved in the original $CrCl_2$-mediated carbonyl olefination with $CHBr_3$ (entry 1). In the absence of NEt_3, the yield of **3a** decreased to 55% (entry 2). Organosilicon compounds other than **1a** resulted in no formation of **3a** (see Supporting Information), similar to the previously reported chromium-catalyzed cyclopropanation with organosilicon compounds.[9] Zinc and manganese powders were much less effective for **3a**, and the β-chloroalkene **3a'** was obtained in both cases (entries 3 and 4). In addition, the catalytic reaction in the presence of $ZnCl_2$ and $MnCl_2$ almost shutdown the catalytic performance even when using **1a** (not detected for $ZnCl_2$; trace for $MnCl_2$, see Supporting Information). We further screened the best additive in this olefination reaction: other sterically different *tert*-amines, ^{i}PrNEt$_2$ and *N*-ethylpiperidine, resulted in almost the same yields as the ligand-free conditions (entries 5 and 6 *vs* entry 2), while the use of pyridine derivatives, 4-(*N,N*-dimethylamino)pyridine (DMAP), suppressed this olefination reaction (entry 7). *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA, 10 mol%) was less effective for this olefination reaction (entry 8), in sharp contrast to the positive effect in Cr-catalyzed cyclopropanation with **1a**,[9] and the addition of 2,2′-bipyridyl (10 mol%) was ineffective for this reaction (entry 9). Further screening of supporting ligands, such as phosphines and carbenes clarified that triethylamine was the most suitable additive for this catalytic system (see Supporting Information).

With the best reaction conditions in hand, we investigated the substrate scope of arylaldehydes with electron-donating and -withdrawing substituents, and the results are summarized in Table 2.

Table 1 Optimization of reaction conditions for Cr-catalyzed olefination of 2-naphthylaldehyde (**2a**) with $CHBr_3$ and **1a**[a]

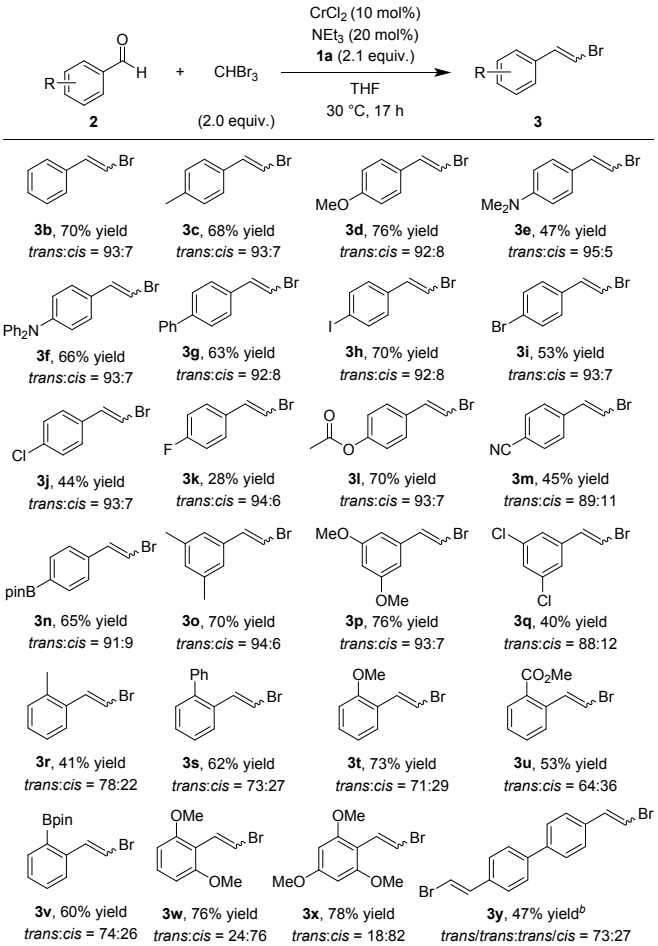


entry	Deviation from the standard conditions	yield of **3a** (%)[b]	*trans*:*cis*[b]
1	-	74[c] (70)[c,d]	93:7
2	Without NEt_3	55	95:5
3[e]	Zn/TMSCl (6.0 equiv.) instead of **1a**	13	92:8
4[f]	Mn/TMSCl (6.0 equiv.) instead of **1a**	25	92:8
5	^{i}PrNEt$_2$ (20 mol%) instead of NEt_3	58	93:7
6	*N*-ethylpiperidine (20 mol%) instead of NEt_3	61	92:8
7	DMAP (20 mol%) instead of NEt_3	28	96:4
8	TMEDA (10 mol%) instead of NEt_3	17	94:6
9	2,2′-bipyridyl (10 mol%) instead of NEt_3	17	94:6

[a] Reaction conditions: Bromoform (0.20 mmol), 2-naphthaldehyde (**2a**, 0.10 mmol), reductant (0.21 mmol for **1a** or 0.60 mmol for Zn and Mn),$CrCl_2$ (0.010 mmol, 10 mol%), and ligand (10-20 mol%) were mixed in THF (2 mL) at 30 °C for 17 h. [b] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] In a 0.40 mmol scale. [d] Isolated yield. [e] *trans*-2-(2-Chlorovinyl)-naphthalene (**3a'**) in 25% yield. [f] **3a'** in 23% yield.

Reactions with benzaldehyde (**2b**) as well as arylaldehydes **2c**,**d** with electron-donating *p*-methyl and *p*-methoxy substituents afforded the corresponding β-bromoalkenes **3b**-**d** in good yields with high *trans* selectivity, whereas *p*-dimethylaminobenzaldehyde (**2e**) was less effective, probably due to an interaction of the dimethylamino moiety with the chromium center, which inhibits the overall reaction. By changing the amino substituent to a less-coordinating diphenylamino group at the 4-position, the corresponding alkene **3f** was isolated in 66% yield. When arylaldehydes **2g**,**h** with weak electron-withdrawing phenyl and iodide groups were used, β-bromoalkenes **3g**,**h** were obtained in good yields and with high *trans* selectivity without loss of the iodide of **3h**. Bromo, chloro, and fluoro groups were tolerated, but the yields decreased with increasing the electronegativity, which might ascribe to the direct reaction of **1a** and the electron-deficient aldehydes during the catalytic reaction, but the details of the byproduct were unclear. Acetate and cyano groups were well tolerated under such reaction conditions to afford *trans*-β-bromoalkenes **3l**,**m** in moderate to good yields. In addition, synthetically useful pinacolatoboryl-substituted aldehyde **2n** was applicable under the catalytic conditions. Olefination of

Table 2 Scope of substituted arylaldehydes in Cr-catalyzed olefination with **1a**[a]



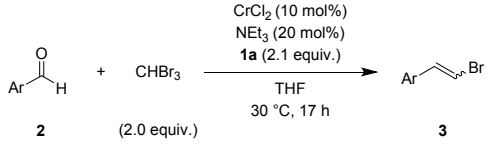
[a] Reaction conditions: Bromoform (0.80 mmol), aldehyde **2** (0.40 mmol), **1a** (0.84 mmol), NEt_3 (0.08 mmol, 20 mol%), and $CrCl_2$ (0.04 mmol, 10 mol%) were mixed in THF (8 mL) at 30 °C for 17 h. [b] Bromoform (1.6 mmol), aldehyde **2y** (0.40 mmol), **1a** (1.7 mmol), NEt_3 (0.16 mmol, 40 mol%), $CrCl_2$ (0.08 mmol, 20 mol%), and THF (12 mL) were used.

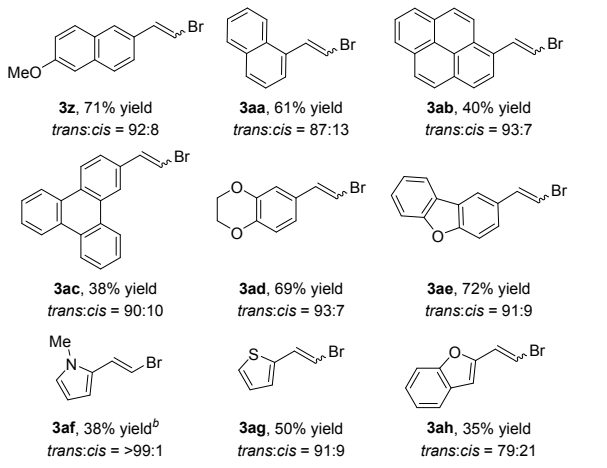
arylaldehydes with substituents at the *meta* and *ortho* positions was further evaluated under the same reaction conditions. Reactions with *meta*-dimethyl and dimethoxy arylaldehydes **2o**,**p** afforded the *β*-bromoalkenes **3o**,**p** in good yields with keeping the high *trans* selectivity, whereas the use of *meta*-dichloro substituted **2q** resulted in a lower yield, a tendency similar to that of *para*-substituted substrates. Stereoselectivity for *ortho*-substituted arylaldehydes was rather different from the *para*- and *meta*-substituted arylaldehydes: treatment with *ortho*-methyl and phenyl-substituted arylaldehydes **2r**,**s** produced *β*-bromoalkenes **3r**,**s** with an increase in the ratio of the *cis*-isomer due to steric congestion. Oxygen-containing substituents at the *ortho*-position, *ortho*-methoxy, methoxycarbonyl, and pinacolatoboryl groups, increased the ratio of the *cis*-isomer with moderate yields. It is noteworthy that the opposite *trans*/*cis* selectivity was observed for *ortho*-disubstituted arylaldehydes, 2,6-dimethoxybenzaldehyde (**2w**) and 2,4,6-trimethoxy-substituted (**2x**), while keeping the high yields of the products **3w**,**x**, suggesting that the methoxy group at the *ortho*-position served as a directing group to the chromium center to increase the *cis*-isomers.[11] In fact, these results were different from the olefination without **1a** under Takai's olefination conditions: the same substrate combination of **2x** and $CHBr_3$ in the presence of excess amounts of $CrCl_2$ afforded the corresponding *trans*-*β*-chloroalkene **3x'** as the major product (29%, *trans*:*cis* = 76:24) together with co-production of **3x** in 19% yield (*trans*:*cis* = 68:32) (see Supporting Information). In addition, the carbonyl olefination of 4,4'-diformylbiphenyl (**2y**) gave **3y** in 47% yield by increasing the reagents to the double amounts.

We further investigated olefination of polycyclic and heterocyclic arylaldehydes under the optimized reaction condtions, as shown in Table 3. 2-Formyl-6-methoxynaphthalene (**2z**) was converted to **3z** in 71% yield without any influence of the methoxy substituent, similar to the reaction with **2d**. Olefination of polycyclic arylaldehydes **2ab**,**ac** as well as 6-formyl-1,4-benzodioxane (**2ad**) gave the corresponding *trans*-*β*-bromoalkenes **3z**-**ad** in moderate to good yields, respectively. 3-Formyldibenzofuran (**2ae**) was also converted to the olefinated product **3ae** in good yield. Five-membered 2-formyl heteroaromatic compounds, *N*-methyl-2-formylpyrrole (**2af**), 2-formylthiophene (**2ag**), and 2-formylbenzofuran (**2ah**) were applicable, and the corresponding *β*-bromoheteroarylalkenes **3af**-**ah** were obtained in low to moderate yields, in which lower *trans* selectivity for **3ah** was ascribed to the oxygen atom adjacent to the formyl group of **2ah**. Of note, **3af** was produced in an exclusive *trans* selective manner. In contrast, 2-formylpyridine was not applicable in this olefination reaction; the corresponding pinacol coupling product was obtained in quantitative yields by **1a** even in the absence of $CrCl_2$ (see Supporting Information).[12]

In addition to $CHBr_3$, other haloforms were applicable to this catalytic olefination (Scheme 1). Olefination of **2a** with $CHCl_3$ afforded the corresponding chloroalkene **3a'** in 42% yield when the reaction temperature was increased to 65 °C due to the lower reactivity for the C-Cl bond fission by $CrCl_2$, while the reaction with CHI_3 gave the corresponding iodoalkene **3a''** in 40% yield at 30 °C. Moreover, olefination of **2a** with $CHCl_2Br$ and $CHClBr_2$ afforded **3a** in 66% yield and 60% yield, respectively, along with the formation of **3a'** as a minor product (see Supporting Information).

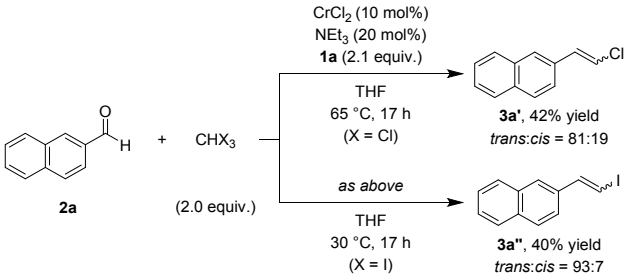
Table 3 Scope of polycyclic and heterocyclic arylaldehydes in Cr-catalyzed olefination with **1a**[a]



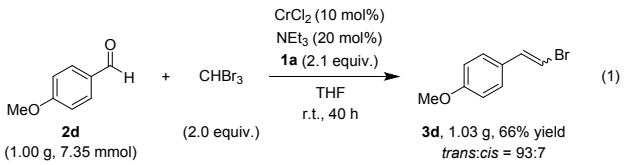


[a] Reaction conditions: Bromoform (0.80 mmol), aldehyde **2** (0.40 mmol), **1a** (0.84 mmol), NEt_3 (0.08 mmol, 20 mol%), and $CrCl_2$ (0.04 mmol, 10 mol%) were mixed in THF (8 mL) at 30 °C for 17 h. [b] Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 1 Scope of haloforms in Cr-catalyzed olefination with **1a**.



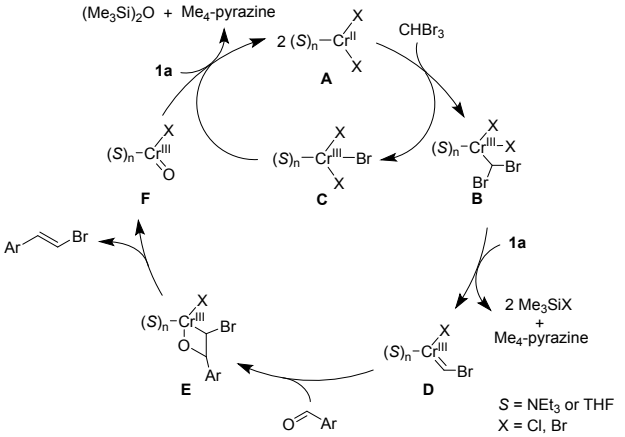
The usefulness of this chromium-catalyzed reaction was demonstrated in the gram-scale synthesis of **3d**. By using 1.00 g of **2d** with bromoform at room temperature for 40 h, the olefination product **3d** was isolated in 66% yield (1.03 g) with keeping the high *trans* selectivity (eq. 1).



According to our previous development on Cr-catalyzed cyclopropanation of alkenes with bromoform,[9] the proposed reaction mechanism for this olefination of arylaldehydes is shown in Scheme 2. Initially, a C-Br bond of $CHBr_3$ is cleaved by chromium(II) species **A** to afford dibromomethylchromium(III) **B** together with co-production of chromium(III) trihalide **C**. Dehalogenation of **B** by **1a** gives chromium(III) bromocarbene intermediate **D**, and a subsequent methathesis type reaction with arylaldehydes generates four-membered oxametallacycle **E**. Fission of the C-O bond in **E**

produces oxochromium(III) halide **F**, and catalytically active chromium(II) species **A** is regenerated *via* reduction of both chromium(III) trihalide **C** and oxochromium(III) halide **F** by **1a**.[13] In this catalytic reaction, **1a** serves as two roles, i.e. regeneration of chromium(II) dihalide **A** as well as dehalogenation of dibromomethylchromium(III) **B**. We presume that the role of NEt_3 in this catalytic reaction is the coordination to the chromium center to inhibit over-reduction to chromium(I) or chromium(0) for initiating uncontrolled reactions with aldehydes. The different stereoselectivity for the olefination of **2x** compared to the $CrCl_2$-mediated olefination reaction by Takai *et al.* suggests that a geminal dichromium species is not involved in this olefination reaction.

Scheme 2 Proposed reaction mechanism.



In summary, we demonstrated that *N,N'*-bis(trimethylsilyl)-2,3,5,6-tetramethyldihydropyrazine (**1a**) served as a salt-free reductant to reduce chromium(III) trihalides as well as a dehalogenating reagent for dibromomethylchromium(III) to generate a chromium(III) bromocarbene intermediate, giving synthetically useful *trans*-β-bromoalkenes upon reaction with aldehydes. A notable feature of this newly developed protocol is the catalytic use of chromium salts without other external metal-based reductants, which eliminates the formation of undesirable and toxic metal salt waste in the reaction mixture. Further application of salt-free reductants in metal-catalyzed organic transformations is ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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