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An Efficient Catalytic Chromium-Mediated Iodocyclopropanation Reaction: Stereoselective Synthesis of Iodocyclopropanecarboxamides

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Abstract: A catalytic chromium-mediated novel synthesis of iodocyclopropanecarboxamides is reported. This reaction can be carried out on aromatic (*E*)- or (*Z*)-α,β-unsaturated amides in which the C=C double bond is di- or trisubstituted. This process takes place with total stereospecificity and the new C–I stereogenic center is generated with high stereoselectivity. Some synthetic applications of the obtained iodocyclopropanecarboxamides are also reported. The structures of the iodocyclopropanes and derivatives were established by X-ray analysis.

Keywords: catalysis; chromium; cyclopropanes; iodocyclopropanes; iron

Chromium dichloride has become an important reagent in synthetic organic chemistry because of its versatility in electron transfer reactions. In the last years, chromium dichloride has been applied to a multitude of organic transformations, which generally proceeded with high selectivity.[1] The only drawback in the use of $CrCl_2$ in organic synthesis is its relatively high price. Thus, methods to carry out transformations using this salt in catalytic amounts would be desirable.

In particular, previous contributions by us (the stereospecific cyclopropanation of α,β-unsaturated amides,[2] the highly stereoselective *tert*-butyl- and silylcyclopropanation[3] and the chloro- and bromocyclopropanation of α,β-unsaturated amides with total or high stereoselectivity[4]) and other[5] laboratories, have demonstrated the utility of $CrCl_2$ for the cyclopropanation of unsaturated compounds. Unfortunately, when the iodocyclopropanation of α,β-unsaturated amides **1** was attempted under the same conditions described for the halocyclopropanation reaction,[4] a 1:3 mixture of the corresponding iodocyclopropanamide **2** and cyclopropanamide **3**, was obtained. These undesirable results could be explained by assuming that, after iodocyclopropanation, the reaction of the excess of $CrCl_2$ with the obtained iodocyclopropanamide could afford an organochromium intermediate, which could be hydrolyzed in the same reaction mixture, giving the corresponding cyclopropanamide **3**.[4]

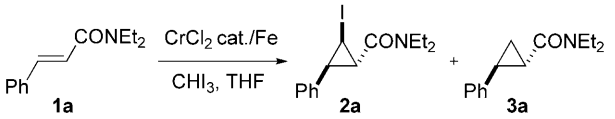
These precedents prompted us to develop a stereoselective iodocyclopropanation of α,β-unsaturated amides using catalytic amounts of $CrCl_2$ rather than stoichiometric quantities. In addition, this method could overcome the drawback of the high price of $CrCl_2$.

In this communication we report a stereoselective synthesis of iodocyclopropanamides **2** with moderate to good stereoselectivity and yields (>62%) from α,β-unsaturated amides **1** using catalytic amounts of $CrCl_2$. As a synthetic application of compounds **2**, we also described the metalation of **2a** with SmI_2 and its stereoselective addition to aldehydes.

To carry out transformations with catalytic $CrCl_2$, a redox system would be necessary to reduce the Cr(III) (generated in the reaction) to Cr(II). In this sense, we attempted the use of Fe for such a purpose due to its ready availability and low price.[6]

The initial reactions were performed using iodoform as iodomethylation agent and *N,N*-diethylcinnamamide **1a** as the model substrate. To op-

Table 1. Initial studies on the iodocyclopropanation of **1a**.



Entry	CHI_3[a]	$CrCl_2$[a]	Fe[a]	T [°C]/t[b]	**2a/3a/1a**[c]
1	1.2	0.42	10.0	55/16 h	2/1/1
2	1.2	0.42	10.0	reflux/16 h	4/2/1
3	3.0	0.42	10.0	55/16 h	2/1/1
4	1.2	0.42	5.0	55/16 h	2/1/4
5	1.2	0.42	10.0	sonication/5 h	2/1/-

[a] Equivalents of reagents.
[b] Reaction time.
[c] Ratio of compounds obtained determined by 300 MHz ^{1}H NMR.

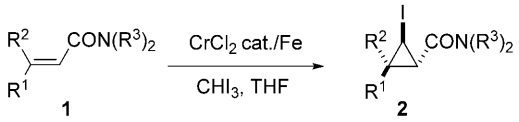
timize the iodocyclopropanation reaction, the reactions shown in Table 1 were performed. The best results were obtained (Table 1, entry 5) sonicating for 5 h a mixture composed of 1 equivalents of cinnamamide **1a**, 1 equivalent of CHI_3, 0.42 equivalent of $CrCl_2$ and 10 equivalents of Fe.

These reaction conditions were used to generalize the process. Thus, a solution of 1 equivalent of the unsaturated amides **1** and CHI_3 (1.0 mmol, 1.0 equiv.) in THF was added to a suspension of anhydrous $CrCl_2$ (0.42 mmol, 0.42 equiv.) and Fe powder (10 mmol, 10 equiv.) in THF. After sonication for 5 h, the reaction mixture was quenched, producing the corresponding iodocyclopropanamides **2** after purification (Table 2). When the reaction was carried out in the absence of $CrCl_2$, no iodocyclopropanation reaction took place and compounds **1** were isolated unaltered.

Analysis of the results compiled in Table 2 indicates that: a) all iodocyclopropanation reactions took place efficiently (62–73% yield) and with good to high stereoselectivity (diastereoisomers ratio ranging from 70/30 to 90/10); b) the reaction was general from aromatic α,β-unsaturated amides, and no important differences were observed when the aromatic ring was substituted with electron-rich or electron-withdrawing groups. When the iodocyclopropanation was performed, under the same reaction conditions, with aliphatic α,β-unsaturated amides, cyclopropanecarboxamides **3** were mainly obtained along with a small amount of the desired compounds **2** (**3/2** ratio 5/1 approximately).

The diastereoisomeric ratio (*dr*) of iodocyclopropylamides **2** was determined by GC-MS and/or 300 MHz ^{1}H NMR analysis of the crude reaction products. These *dr* values should be analyzed taking into account that there are three stereogenic centers in iodocyclopropanamides **2**, one of them being generated during the reaction.

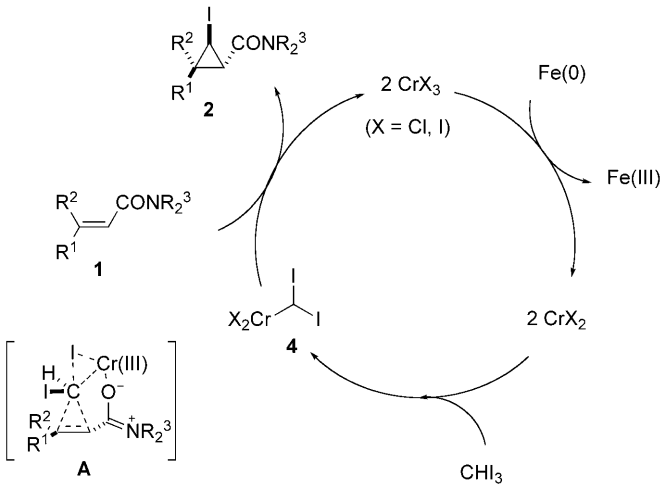
Table 2. Synthesis of Iodocyclopropanecarboxamides **2**.



Entry	**2**	R^1	R^2	$N(R^3)_2$	*dr*	Yield [%][a]
1	**2a**	Ph	H	NEt_2	90/10	69
2	**2b**	H	Ph	NEt_2	80/20	67
3	**2c**	Ph	H	$N(i\text{-Pr})_2$	80/20	61
4	**2d**	Ph	H	–[b]	80/20	71
5	**2e**	*p*-$MeOC_6H_4$	H	NEt_2	75/25	70
6	**2f**	*o*-$MeOC_6H_4$	H	NEt_2	71/29	68
7	**2g**	*p*-$CF_3C_6H_4$	H	NEt_2	75/25	66
8	**2h**	*o*-$CF_3C_6H_4$	H	NEt_2	70/30	67
9	**2i**	*p*-FC_6H_4	H	NEt_2	75/25	63
10	**2j**	*m*-HOC_6H_4	H	NEt_2	75/25	62
11	**2k**	Ph	Et	NEt_2	81/15	73

[a] Yield of the corresponding isolated products **2** based on compounds **1**.
[b] From morpholine.

The structures and relative configurations of iodocyclopropylamides (as depicted in Table 2 and Scheme 1) were established by analysis of the ^{1}H NMR coupling constants between the cyclopropane protons of amides **2**, by NOE experiments of compounds **2a**, **2b**, **2d**, **2e**, **2h**, **2j**, **2k** and single-crystal X-ray analysis of compounds **2b**, and **2d**.[7] The NOE experiments in compounds **2b** and **2d** were in agreement with the X-ray structures. It is important to note that the relative configuration of the C=C double bond of the starting amides was conserved during the cyclopropanation. The conservation of the C=C geometry was unambiguously established by performing the reaction from the diastereoisomers (*E*)- and (*Z*)-cinnamamide **1a** and **1b** (Table 2, entries 1 and 2). No



Scheme 1. Mechanistic proposal.

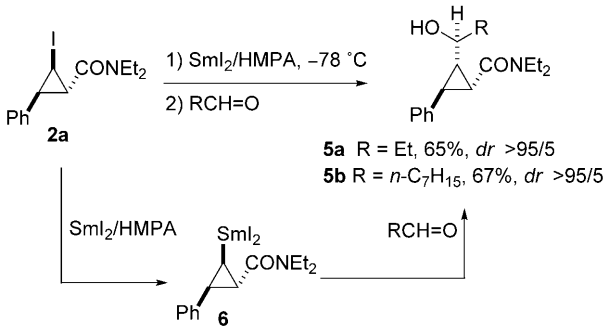
important differences were observed from these diastereoisomers, and the relative positions of the R^1 and amide groups in **1a** and **2a** or in **1b** and **2b** were the same. The stereogenic centers generated in the halocyclopropanations (CH–I, CH–Br and CH–Cl) were obtained with the same relative configurations.[4] In all cases, the iodine atom adopted a *trans* position with respect to the carboxamide.

This iodocyclopropanation process could be explained assuming the initial formation of a chromium-(III) carbenoid intermediate **4**, after the reaction of 2 equivalents of $CrCl_2$ with 1 equivalent of CHI_3. This anion could react with α,β-unsaturated amides **1** to give the corresponding iodocyclopropane **2**, through a similar mechanism to that proposed by Houk for the addition of carbenoids to olefins.[9]

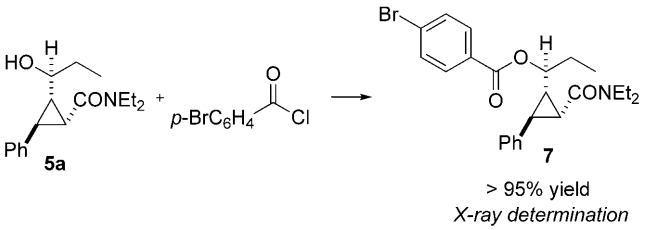
A coordination of the Cr(III) center with the oxygen atom of the amide group could explain the observed conservation of the C=C geometry.[10] Tentatively, we propose transition state model **A** depicted in Scheme 1, in which the formation of the new stereogenic center with total or high stereoselectivity could be explained based on the steric hindrance between the iodine atom and the amide group. To minimize the steric hindrances, the iodine atom could occupy a *trans* relative position with respect to the amide function. This relative configuration was in agreement to that observed in the previously reported chloro- or bromocyclopropanation of α,β-unsaturated amides.[4] Once compound **2** is generated, the chromium(III) species are then reduced with iron(0) to produce more chromium(II).

The obtained iodocyclopropanamides **2** can be versatile starting materials, due to their high functionality. To illustrate this synthetic possibility, metallation of compound **2a** with SmI_2 in the presence of HMPA at −78 °C, was carried out.[11] The obtained organosamarium **6** was allowed to react with propanal and octanal and to afford compounds **5a** and **5b** with total stereoselectivity[12] (Scheme 2).

The relative configuration of compounds **5** was unambiguously assigned based on the studies of single-crystal X-ray diffraction.[13] Since no crystallization of



Scheme 2. Synthetic application of compound **2a**.



Scheme 3. Derivatization of **5a** for X-ray determination.

compounds **5** has been possible, treatment of **5a** with *p*-bromobenzoyl chloride, was carried out (Scheme 3). Thus, **5a** afforded the corresponding ester **7** in nearly quantitative yield, which was utilized to confirm the structure for **5**.

These structures were compatible with a metallation reaction of the C–I bond performed by SmI_2 with total retention of its configuration. Thus, the addition reaction of the generated anion **6** to the corresponding aldehyde also took place with total stereoselectivity, since only one diastereoisomer of compounds **5** was observed.[5]

In conclusion, we have described a novel and efficient iodocyclopropanation reaction of a variety of α,β-unsaturated amides **1** under very mild conditions, promoted by catalytic amounts of $CrCl_2$ to afford 1-(2-iodo-3-arylcyclopropyl)amides **2** from moderate to good stereoselectivity and high yields. The synthetic applications of compounds **2** were tested by generating the corresponding organosamarium compound *via* treatment of iodocyclopropanecarboxamide **2a** with SmI_2/HMPA. The addition of this intermediate to aldehydes afforded compounds **5** with total stereoselectivity.

Studies directed toward fully delineating the factors involved in the $CrCl_2$-mediated catalytic syntheses and the generality of the transformations of iodocyclopropanamides in other valuable compounds are currently in progress in our laboratory.

Experimental Section

Synthesis of Products 2

To a suspension of anhydrous $CrCl_2$ (0.42 mmol, 0.42 equiv.) and Fe powder (10 mmol, 10 equiv.) in THF (6 mL) was added the corresponding α,β-unsaturated amide **1** (1.0 mmol, 1.0 equiv.) in THF (3 mL) and CHI_3 (1.0 mmol, 1.0 equiv.) in THF (3 mL) at room temperature and under an inert atmosphere. After sonication for 5 h the reaction mixture was quenched by the addition of 1.0 M aqueous HCl (5 mL) and extracted with diethyl ether (3×10 mL). The combined extracts were washed with saturated NH_4Cl solution and an aqueous sodium thiosulfate solution, dried over Na_2SO_4, and concentrated under vacuum. Purification

by column chromatography on silica gel (hexane/EtOAc 5:1) afforded pure compounds **2.**

Synthesis of Compounds 5

The synthesis of compounds **5a**, **5b** was carried on according the procedure described in ref.[10]

Synthesis of Products 7

To a suspension of 4-bromobenzoyl chloride (0.4 mmol, 1 equiv.) in CH_2Cl_2 (4 mL) was added theNEt_3 (0.8 mmol, 2 equiv.) and a catalytic amount of DMAP (5 mg). The alcohol **5a** (0.4 mmol, 1 equiv.) was added dropwise with cooling in a bath of ice-water and under an inert atmosphere. After stirring of the mixture for 16 h the reaction was quenched by the addition of H_2O and extracted with CH_2Cl_2 (3× 5 mL). The combined extracts were washed with HCl (1.0 M), dried over Na_2SO_4 and concentrated under vacuum. Purification of the product was carried on by column chromatography on silica gel (hexane/EtOAc 5:1).

Acknowledgements

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[6] Some co-reductants have been employed to perform transformations in which catalytic amounts of $CrCl_2$ were utilized.

[7] CCDC 780481 and CCDC 780482 contain the supplementary crystallographic data for compounds **2b** and **2d**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif [or from the Cambridge Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax (+44)-1223-336-033; or deposit@ccdc.cam.ac.uk].

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[9] Other alternative mechanism involving a chromium carbene complex cannot be discarded. So, synthesis of **2** can be explained assuming a [2+2] addition reaction of the corresponding chromium alkylidene specie IHC=Cr followed by a reductive elimination from the generated chromacyclobutane, see refs.[3b,5b]

[10] A similar transition state **A** (based on steric interactions) has been previously used to justify the synthesis and stereochemistry of the alkyl-, silyl-, and halo-cyclopropanation of α,β-unsaturated amides (see refs.[3,4]).

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[12] The presence of only one diastereoisomer was established by GC-MS, and/or 300 MHz ^{1}H NMR analysis of the crude reaction product.

[13] CCDC 780482 contains the supplementary crystallographic data for compound **7**. These data can be obtained free of charge, see ref.[7].

