

An Efficient Method for the Copper(II)-promoted Stereoselective Iodofunctionalization of Alkenes¹

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A mixture of iodine and CuO·HBF₄ reacts stereoselectively with alkenes in the presence of a wide variety of nucleophiles (water, MeOH, HCO₂H, AcOH, EtCO₂H, NaNO₂, KSCN, NaSO₂Ar, LiCl, LiBr, NaI, Et₃SiH, and MeOPh) to give the corresponding 2-functionalized iodo compounds. A regio-chemistry study is also reported.

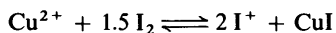
Copper compounds have been widely used in organic chemistry: copper(II) ions as oxidation reagents for different systems,² copper(I) salts as catalysts of C–C bond formation,³ and organocopper compounds in addition or substitution reactions.⁴ Furthermore, the low toxicity of this metal and the presence of copper in biohalogenation enzymes⁵ have increased the importance of copper compounds in the biosynthetic field.

Copper(II) ions are commonly used as promoters in electrophilic halogenations⁶ of a wide variety of organic systems: carbonyl compounds,^{7,8} carboxylic acids,⁹ aromatic rings,^{8,10} alkenes,^{11–14} conjugated dienes,¹⁴ and alkynes.^{13,15} When alkenes or alkynes are the substrates in those halogenations the scope of the reaction is limited by the addition of the counter-ion of the Cu^{II} salt (Cl[−] or Br[−]) as nucleophile to the multiple C–C bond; compounds which undergo this reaction process only a limited number of other functional groups.¹⁶ Mixtures were obtained in practically all the known examples of halogenofunctionalization promoted by copper(II) and the synthetic potential was therefore low.

In recent years, we have researched the iodofunctionalization of different systems promoted by bis(pyridine)iodine(I) tetrafluoroborate.¹⁷ We have also described an alternative to our reagent, one which allows the iodofunctionalization of alkenes, dienes, and alkynes with a mixture of iodine and CuO·HBF₄ in the presence of nucleophiles.¹ The wide interest in halogenations with copper(II) salts and the simplicity and the mildness of the reaction conditions encouraged us to investigate the regio- and stereo-chemistry of the addition to a range of alkenes.

Results and Discussion

The low nucleophilicity of the counter-anion of the copper(II) ion used here (tetrafluoroborate) allows a wide variety of charged (Cl[−], Br[−], I[−], NO₂[−], *p*-MeC₆H₄SO₂[−], NCS[−]) as well as uncharged nucleophiles (water, MeOH, HCO₂H, MeCO₂H, EtCO₂H, Et₃SiH, C₆H₅OMe) to be added to the alkene. The stoichiometric ratios of the reagents were determined by the formation of electrophilic iodine I⁺ according to the equilibrium showed in Scheme 1.¹⁴ Positive iodine reacts with the alkene and this is followed by addition of the nucleophile to give a 1,2-iodo-functionalized product and a light brown precipitate of copper(I) iodide.



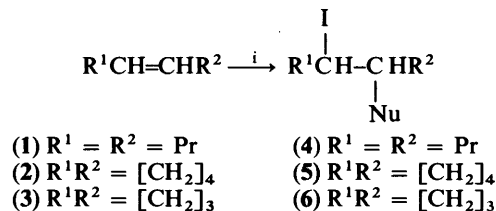
Scheme 1.

Very low concentration of I⁺ was present at room

temperature, as was demonstrated by treatment of a suspension of copper(I) iodide in dichloromethane with a solution of bis(pyridine)iodine(I) tetrafluoroborate. The precipitate rapidly dissolved and molecular iodine and copper(II) ions were formed.

How the reagent, CuO·HBF₄, was used depended on the nucleophile. When the nucleophile was water, formic acid (85% aq. solution), lithium chloride, lithium bromide, sodium nitrite, sodium toluene-*p*-sulphonate or potassium thiocyanate, the blue solution which resulted from admixture of tetrafluoroboric acid (35% aq. solution) (2 mol equiv.) with copper(II) oxide (1 mol equiv.) was directly used (method A, see Table and Experimental section). In the reactions with methanol, acetic or propionic acids, sodium iodide, or triethylsilane as nucleophile the blue solution must be evaporated at reduced pressure (10^{−2} mmHg and 50–60 °C) to constant weight, in order to prevent the competition of water as a nucleophile. The pale blue solid thus obtained was used as the reagent (method B, see Table and Experimental section). The water of crystallization present in this copper(II) tetrafluoroborate¹⁸ produced important side-reactions when anisole was assayed as nucleophile. To avoid this problem, copper(II) oxide was mixed with silica gel and dissolved in 35% aq. tetrafluoroboric acid. The mixture was evaporated to dryness under reduced pressure and the resulting CuO·HBF₄, supported on silica gel, was used in the iodocarbonylation of olefins.

The reaction of an alkene (2 mol equiv.) with a mixture of iodine (1.5 mol equiv.) and an excess of nucleophile at room temperature gives, in a clean 'one-pot' single-step process, the corresponding *trans*-1,2-iodofunctionalized product stereoselectively (Scheme 2, Table). The stereochemistry of the product (4)–(6) was determined by comparison of its spectral data with our previous data.^{19,20}



Scheme 2. Reagents: i, CuO·HBF₄, I₂, NuH or Nu[−].

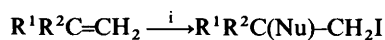
The Markovnikov regioisomer was exclusively obtained with styrene and 2-methylpent-1-ene (Scheme 3, Table) but monosubstituted alkenes (hex-1-ene) gave an equimolar mixture of two regioisomers (Scheme 4, Table).

These regio- and stereo-chemical results are identical with those obtained in electrophilic iodofunctionalization of alkenes

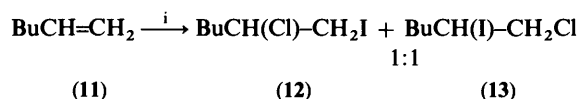
Table. Iodofunctionalization of alkenes.

Substrate	Nucleophile (Nu)	Solvent	Method	t/h	Product	Yield (%) ^a
(1)	water (HO) ^b	MeCN	A	3	(4)	60
(2)	water (HO) ^b	MeCN	A	4	(5a)	74
(2)	MeOH (MeO)	MeOH	B	4	(5b)	80
(2)	HCO ₂ H (HCO ₂) ^c	CH ₂ Cl ₂ -HCO ₂ H (5:1)	A	2	(5c)	70
(2)	AcOH (AcO)	CH ₂ Cl ₂ -AcOH (5:1)	B	0.5	(5d)	95
(2)	EtCO ₂ H (EtCO ₂)	CH ₂ Cl ₂ -EtCO ₂ H (5:1)	B	1	(5e)	92
(2)	NaNO ₂ (O ₂ N)	Dioxane	A	2	(5f)	44
(2)	KSCN (NCS)	MeCN	A	4	(5g)	75
(2)	<i>p</i> -MeC ₆ H ₄ SO ₂ Na (<i>p</i> -MeC ₆ H ₄ SO ₂)	MeCN	A	4	(5h)	95
(2)	LiCl (Cl)	MeCN	A	4	(5i)	77
(2)	LiBr (Br)	MeCN	A	4	(5j)	66
(2)	NaI (I) ^d	CH ₂ Cl ₂	B	4	(5k)	79
(2)	Et ₃ SiH (H) ^d	CH ₂ Cl ₂	B	3	(5l)	95
(2)	anisole (<i>p</i> -MeOC ₆ H ₄) ^e	CH ₂ Cl ₂	B	13	(5m)	30 ^f
(3)	water (HO) ^b	MeCN	A	3	(6a)	55
(3)	MeOH (MeO)	MeOH	B	3	(6b)	75
(3)	LiCl (Cl) ^b	MeCN	A	6	(6i)	62
(7)	water (HO) ^b	MeCN	A	2	(9a)	65
(7)	MeOH (MeO)	MeOH	B	2	(9b)	85
(7)	AcOH (AcO)	CH ₂ Cl ₂ -AcOH (5:1)	B	1	(9d)	89
(7)	KSCN (NCS)	MeCN	A	4	(9g)	42
(8)	water (HO) ^b	MeCN	A	5	(10)	75
(11)	LiCl (Cl)	MeCN	A	2	(12)/(13) ^g	77 (1/1) ^h

^a Yield of isolated product, relative to starting alkene and not optimized. ^b From starting aq. copper(II) solution. ^c 85% aq. solution. ^d Mole ratio nucleophile:alkene 2:1. ^e Mole ratio nucleophile:alkene 1:1. ^f Purified by column chromatography (silica gel; hexane-diethyl ether, 98:2). ^g The regioisomers could not be separated. ^h Isomer ratio, determined by GLC.



Scheme 3. Reagents: *i*, CuO·HBF₄, I₂, NuH or Nu⁻.



Scheme 4. Reagents: *i*, CuO·HBF₄, I₂, LiCl, MeCN.

by bis(pyridine)iodine(I) tetrafluoroborate,^{17,19} and we therefore propose an analogous mechanism involving a cyclic iodonium ion intermediate in the copper-promoted iodofunctionalization of alkenes.

All compounds were previously reported; (5k),²¹ (12) and (13),¹² and the remaining products are reported in our earlier papers on iodofunctionalization of alkenes.^{19,20} *trans*-1,2-Diiodocyclohexane (5k) has already been described;²¹ however, the spectral data were not previously reported. We have achieved an addition of iodine to cyclohexene in high yield and short reaction time with complete characterization of the product (5k).

We have described a general method for the iodofunctionalization of alkenes under mild conditions, and the method is applicable to a wide range of nucleophiles.

Experimental

¹H and ¹³C NMR spectra were recorded on a Varian FT-80 A

or a Bruker AC-300 spectrometer and the chemical shifts are given relative to internal SiMe₄ standard. Mass spectra were run on an HP 5987 A apparatus. GLC analyses were carried out on a Varian Vista 6000 gas chromatograph with a OV-101 column. Reagents and solvents were commercial grades (from Merck and Aldrich).

General Procedure for Electrophilic Addition to Alkenes.—
Method A. To a solution of copper(II) tetrafluoroborate (1.62 ml, 8 mmol), prepared from 35% aq. HBF₄ and CuO (0.32 g, 4 mmol), were added the corresponding solvent (20 ml) and nucleophile (20 mmol) (see Table). After the mixture had been stirred for 2 min, iodine (1.52 g, 6 mmol) and the alkene (8 mmol) were introduced into the reaction flask and the mixture was stirred at room temperature. The precipitated copper(I) iodide was filtered off after addition of water (25 ml), and the filtrate was extracted with CH₂Cl₂ (3 × 25 ml), washed with 5% aq. sodium thiosulphate (25 ml) [and 5% aq. NaHCO₃ (2 × 25 ml) when the nucleophile was an organic acid], dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The resulting crude materials were essentially pure compounds (GLC purity > 90%).

Method B. A similar aq. solution of copper(II) tetrafluoroborate was evaporated at 10⁻² mmHg and 50–60 °C to constant weight, to yield a pale blue solid [for compound (5m) silica gel (2 g) was added before evaporation]. This was added to a mixture of solvent (20 ml), nucleophile (see Table), iodine (1.52 g, 6 mmol), and substrate (8 mmol), at room temperature under argon. After being stirred, the solution was hydrolysed and treated as in method A. The resulting crude materials were essentially pure compounds (GLC purity > 90%). Only compound (5m) required purification by column chromatography (silica gel; hexane-diethyl ether, 98:2).

trans-1,2-Diiodocyclohexane (5k) was obtained as a viscous oil, δ_H(CDCl₃) 1.1–2.4 (m, 8 H) and 4.9–5.0 (m, 2 H); δ_C(CDCl₃) 25.4 (t), 34.8 (d), and 41.5 (t).

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