C–H Activation

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Hydroxoiridium-Catalyzed Hydroalkylation of Terminal Alkenes with Ureas by C(sp^3)–H Bond Activation

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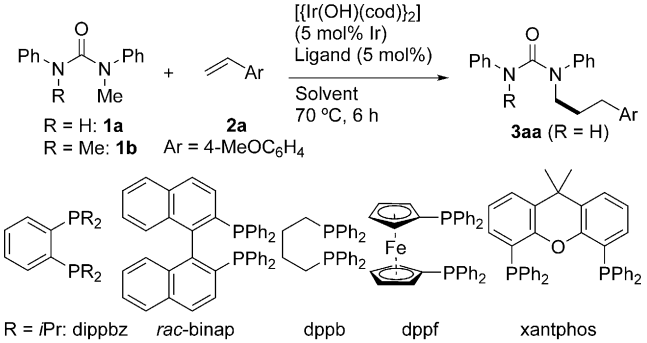
Abstract: *Direct alkylation of a methyl group, on di- and trisubstituted ureas, with terminal alkenes by C(sp^3)–H bond activation proceeded in the presence of a hydroxoiridium/bisphosphine catalyst to give high yields of the corresponding addition products. The hydroxoiridium/bisphosphine complex generates an amidoiridium intermediate by reaction with ureas having an N–H bond.*

Recent rapid progress in transition-metal-catalyzed direct functionalization reaction of unactivated C–H bonds has opened up new possibilities for achieving highly atom-efficient transformations in synthetic organic chemistry.[1] Although many studies have realized the reactions by C(sp^2)–H activation, selective C(sp^3)–H functionalization is still a challenging objective in this field.[2] The alkylation of C(sp^3)–H bonds with alkenes is obviously one of the useful C–C bond formation reactions, and in view of the site selectivity of the C–H bond activation, the alkylation of the C(sp^3)–H bonds adjacent to a nitrogen center[3] has been developed by using transition-metal catalysis[4–8] as well as radical reactions.[9,10] With respect to the directed C(sp^3)–H alkylation catalyzed by late transition metals, ruthenium-catalyzed alkylations of the C(sp^3)–H bond of 2-(*N*-alkylamino)pyridines with alkenes were reported by the groups of Jun[5a] and Murai,[5b] independently. Shibata and co-workers have developed enantioselective hydroalkylation of alkenes by secondary C(sp^3)–H bond activation of *N*-2-(alkylamino)-pyridines catalyzed by cationic iridium/chiral bis(phosphine) complexes.[6b,c,e]

Recently, we reported that a hydroxoiridium/chiral diene complex catalyzes asymmetric alkylation of *N*-sulfonylbenzamides with vinyl ethers.[11] The reaction involves an amidoiridium(I) species as a key intermediate derived from the neutral hydroxoiridium and benzamide, and the key species undergoes oxidative addition of an *ortho*-C–H bond to form an aryl(hydrido)iridium(III) species. We also reported asymmetric hydroarylation of vinyl ethers using aryl-substituted azoles, containing an N–H bond as a directing group, catalyzed by a hydroxoiridium/chiral bis(phosphine) complex.[12] The reaction also involves the formation of an amidoiridium species as an essential intermediate. In this context, we found that ureas are suitable substrates in forming the amidoiridium species for the activation of the C(sp^3)–H bond of a methyl group adjacent to a nitrogen center. Herein we report that a hydroxoiridium/bis(phosphine) complex can catalyze the hydroalkylation reaction of terminal alkenes with ureas by C(sp^3)–H bond activation. The method provides an easy access to biologically active compounds containing an amino group or a urea moiety.[13]

Treatment of 1-methyl-1,3-diphenylurea (**1a**) with 4-methoxystyrene (**2a**) in the presence of [{Ir(OH)(cod)}$_2$] (5 mol% of Ir, cod = 1,5-cyclooctadiene) and 1,2-bis(diisopropylphosphino)benzene (dippbz; 5 mol%) in 1,4-dioxane at 70 °C for 6 hours gave the hydroalkylation product **3aa** in 92% yield (Table 1, entry 1). The alkylation occurred at the methyl group and the other possible reaction sites, such as the *ortho* positions of the two benzene rings, were inert. Bidentate triarylphosphine ligands, 1,2-bis(diphenylphosphino)benzene (dppbz), and *rac*-binap, were less effective than dippbz (entries 2 and 3). The use of dppb, dppf, and xantphos resulted

Table 1: Iridium-catalyzed hydroalkylation of **2a** with the ureas **1**.[a]



Entry	Ligand	Solvent	1	Yield [%][b]
1	dippbz	1,4-dioxane	**1a**	92
2	dppbz	1,4-dioxane	**1a**	4
3	*rac*-binap	1,4-dioxane	**1a**	26
4	dppb	1,4-dioxane	**1a**	0
5	dppf	1,4-dioxane	**1a**	0
6	xantphos	1,4-dioxane	**1a**	0
7	–	1,4-dioxane	**1a**	31
8[c]	dippbz	1,4-dioxane	**1a**	0
9	dippbz	1,4-dioxane	**1b**	0
10	dippbz	toluene	**1a**	49
11	dippbz	MeCN	**1a**	12
12	dippbz	1,2-dichloroethane	**1a**	0

[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.12 mmol), [{Ir(OH)(cod)}$_2$] (5 mol% of Ir), and ligand (5 mol%) in 1,4-dioxane (0.1 mL) at 70 °C for 6 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Performed with [{IrCl(cod)}$_2$] (5 mol% of Ir) and NaBAr$^F_4$ (10 mol%) instead of [{Ir(OH)(cod)}$_2$].

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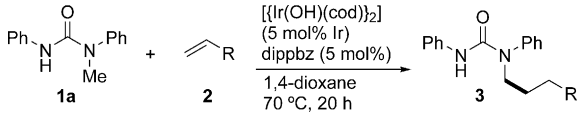
in no formation of the addition product (entries 4–6). [{Ir(OH)(cod)}$_2$] itself displayed a low catalytic activity in the absence of dippbz, thus giving **3aa** in 31% yield (entry 7). A cationic complex generated from [{IrCl(cod)}$_2$], dippbz, and $NaBAr^F_4$ [Ar^F = 3,5-$(CF_3)_2C_6H_3$] had no catalytic activity (entry 8). In addition, the reaction of 1,3-dimethyl-1,3-diphenylurea (**1b**) did not take place under the present catalytic conditions (entry 9). These results indicate that the formation of the amidoiridium species from the hydroxoiridium and trisubstituted urea is essential for the present reaction. The reaction in toluene gave the addition product in 49% yield (entry 10), while the other solvents such as acetonitrile and 1,2-dichloroethane were ineffective (entries 11 and 12).

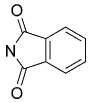
Table 2 summarizes the results obtained for the hydroalkylation of several terminal alkenes **2** with 1-methyl-1,3-diphenylurea (**1a**). The *para*-substituted styrenes with electron-donating (MeO, Me) and electron-withdrawing groups (Cl, Br) are all good substrates for giving the corresponding addition products **3aa**–**ae** in high yields (entries 1–5). The reaction of 2,3,4,5,6-pentafluorostyrene (**2f**) required a higher catalyst loading because of the slow reaction and catalyst deactivation (entry 6). The *meta*- and *ortho*-methoxy-substituted styrenes **2g** and **2h**, respectively, also reacted with **1a** to give the corresponding **3ag** and **3ah** in high yields (entries 7 and 8). The reactions of 1-octene (**2i**) and vinylcyclohexane (**2j**) proceeded to give the corresponding adducts **3ai** and **3aj**, respectively, in high yields, although the use of two equivalents of alkenes was needed because of the isomerization of the alkene moieties (entries 9 and 10). The vinyl silane **2k**, vinyl ether **2l**, and *N*-vinyl amide **2m** and imide **2n** also reacted with **1a** to give the addition products in good yields (entries 11–14). The reaction of an electron-deficient alkene, diethyl vinylphosphonate (**2o**), gave **3ao** in 83% yield (entry 15), while ethyl acrylate (**2p**) was less reactive, thus resulting in 39% yield of the adduct **3ap**, even in the presence of 10 mol% of the Ir/dippbz catalyst (entry 16). Isoprene (**2q**) also reacted with **1a** to give rise to addition product **3aq** in 80% yield, where the vinyl group of isoprene selectively participated in the reaction (entry 17).

The present catalytic system was also applicable to the reactions of several ureas (**1**) with *para*-methoxystyrene (**2a**; Table 3). A variety of functional groups on aromatic rings (X) of the ureas were tolerated in the reaction, thus giving high yields of the adducts **3ca**–**ka** (entries 1–9). The ureas having alkyl groups (Y) adjacent to the *N*-methyl moiety reacted with **2a** in the presence of $KOSiMe_3$, as a base, to give

Table 2: Iridium-catalyzed hydroalkylation of the alkenes **2** with **1a**.[a]

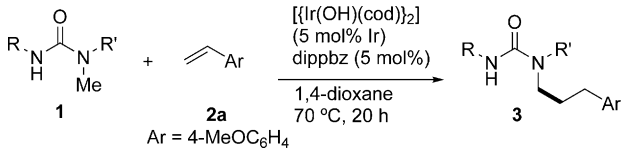


1a + **2** → **3**

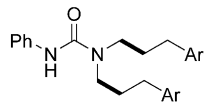
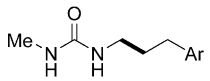
Entry	2	R	3	Yield [%][a]
1	**2a**	4-$MeOC_6H_4$	**3aa**	95
2	**2b**	Ph	**3ab**	92
3	**2c**	4-MeC_6H_4	**3ac**	99
4	**2d**	4-ClC_6H_4	**3ad**	95
5	**2e**	4-BrC_6H_4	**3ae**	93
6[b]	**2f**	C_6F_5	**3af**	87
7[c]	**2g**	3-$MeOC_6H_4$	**3ag**	91
8[c]	**2h**	2-$MeOC_6H_4$	**3ah**	93
9[d,e]	**2i**	*n*-hexyl	**3ai**	88
10[d,e]	**2j**	*c*-hexyl	**3aj**	88
11	**2k**	$SiEt_3$	**3ak**	93
12[d,f]	**2l**	O*n*Bu	**3al**	72
13[c]	**2m**		**3am**	89
14[b,f]	**2n**		**3an**	83
15[b,d,f]	**2o**	$PO(OEt)_2$	**3ao**	83
16[b,d,f]	**2p**	CO_2Et	**3ap**	39
17[e]	**2q**	$C(CH_3)=CH_2$	**3aq**	80

[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.24 mmol), [{Ir(OH)(cod)}$_2$] (5 mol% of Ir), and dippbz (5 mol%) in 1,4-dioxane (0.2 mL) at 70°C for 20 h. Yield is that of the isolated product. [b] [{Ir(OH)(cod)}$_2$] (10 mol% of Ir) and dippbz (10 mol%) were used. [c] For 48 h. [d] Performed with toluene (0.2 mL). [e] **2** (0.40 mmol) was used. [f] At 80°C.

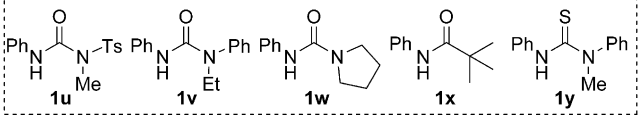
Table 3: Iridium-catalyzed hydroalkylation of **2a** with the ureas **1**.[a]



1 + **2a** (Ar = 4-$MeOC_6H_4$) → **3**

Entry	1	3	Yield [%][a]
1[b]	**1c** (X = 4-MeC_6H_4)	**3ca**	85
2[b]	**1d** (X = 4-$MeOC_6H_4$)	**3da**	91
3[c]	**1e** (X = (4-morpholino)C_6H_4)	**3ea**	91
4	**1f** (X = 4-ClC_6H_4)	**3fa**	84
5[b]	**1g** (X = 4-BrC_6H_4)	**3ga**	87
6	**1h** (X = 4-$(CO_2Et)C_6H_4$)	**3ha**	93
7	**1i** (X = 3-MeC_6H_4)	**3ia**	95
8	**1j** (X = 2-MeC_6H_4)	**3ja**	98
9	**1k** (X = 1-naphthyl)	**3ka**	96
10[d]	**1l** (Y = *n*-butyl)	**3la**	90
11[c,d]	**1m** (Y = *c*-hexyl)	**3ma**	77
12[d]	**1n** (Y = Bn)	**3na**	88
13	**1o** (Z = 4-MeC_6H_4)	**3oa**	96
14	**1p** (Z = 4-ClC_6H_4)	**3pa**	87
15[e]	**1q** (Z = Me)	**3qa**	60
16[e]	**1r** (Z = Bn)	**3ra**	37
17[f]	 **3sa**: 95%		
18	 **3ta**: 88%		

unreactive substrates



[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.24 mmol), [{Ir(OH)(cod)}$_2$] (5 mol% of Ir), and dippbz (5 mol%) in 1,4-dioxane (0.2 mL) at 70°C for 20 h. Yield is that of isolated product. [b] For 48 h. [c] At 80°C. [d] Me_3SiOK (10 mol%) was added. [e] Performed in toluene (0.2 mL). [f] **2a** (0.48 mmol) was used. Ts = *p*-toluenesulfonyl.

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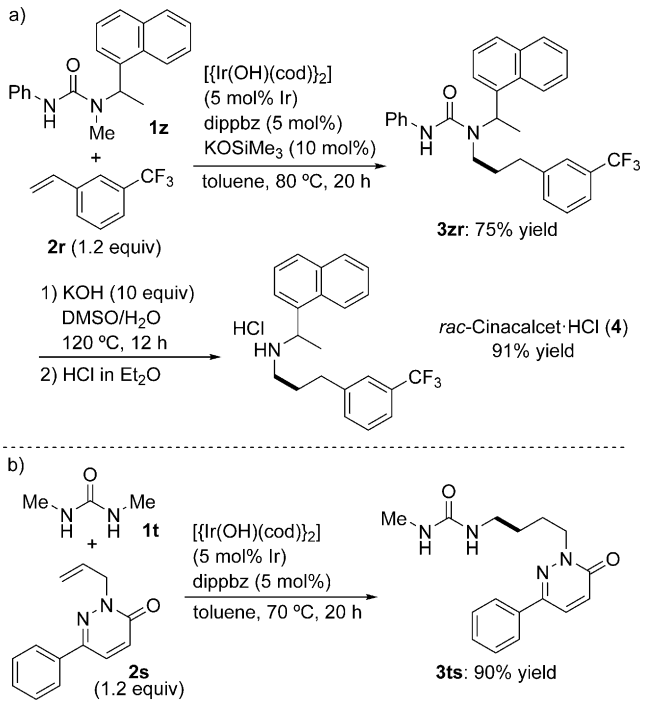
addition products **3la**–**na** (entries 10–12).[14] The reactivity of the *N*-methyl-*N*-phenyl ureas **1o** and **1p**, having aryl groups (Z) at another nitrogen atom, was high (entries 13 and 14), while the alkyl-substituted ureas **1q** and **1r** displayed relatively low reactivity (entries 15 and 16). Double alkylation of 1,1-dimethyl-3-phenylurea (**1s**) with **2a** proceeded to give **3sa** in 95% yield (entry 17). 1,3-Dimethylurea (**1t**) is also a good substrate to undergo the alkylation with **2a**, thus giving **3ta** in 88% yield (entry 18). The reaction did not take place at all with **1u**, which has a tosyl group on the nitrogen atom. The alkylation of a secondary alkyl C–H bond of either **1v** or **1w** was not observed, and neither *N*-phenylpivalamide (**1x**) nor the thiourea **1y** were reactive under the present catalytic conditions.

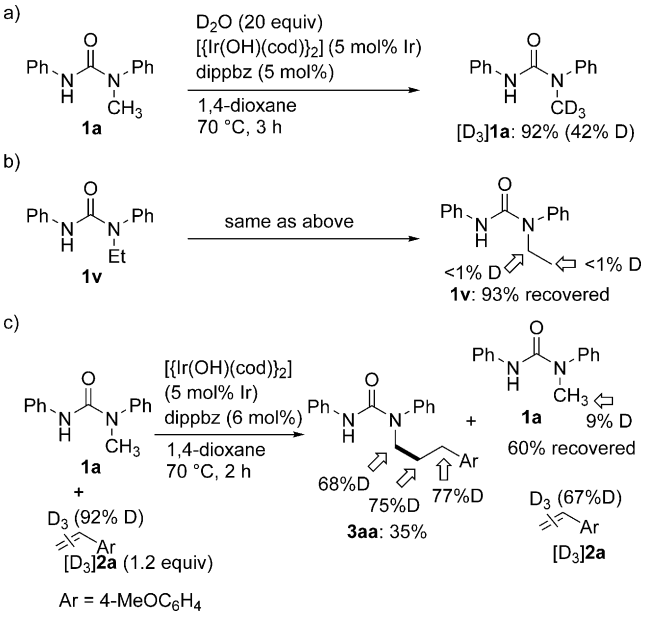
The present alkylation reaction can be applied to the straightforward synthesis of some biologically active compounds (Scheme 1). For example, the reaction of the urea **1z**



Scheme 1. Synthesis of biologically active compounds. DMSO = dimethyl sulfoxide.

with 3-(trifluoromethyl)styrene (**2r**) gave the alkylation product **3zr** in 75% yield. Hydrolysis of **3zr** by aqueous KOH gave the corresponding amine, and then, treatment of the resulting amine with HCl in Et_2O gave *rac*-Cinacalcet hydrochloride (**4**), which is a drug that acts as a calcimimetic agent (Scheme 1a).[15] The urea **3ts**, which shows an antisecretory and antiulcer activities, was prepared from 1,3-dimethylurea (**1t**) and the *N*-allylpyridazinone **2s** in 90% yield (Scheme 1b).[16]

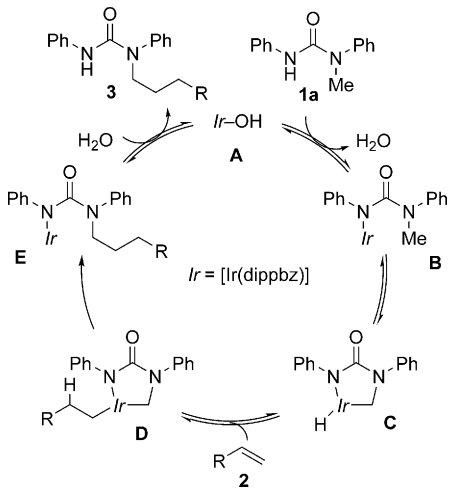
C–H activation under the present catalytic system was found to occur only at the methyl group of **1a** (Scheme 2a). Thus, treatment of **1a** with D_2O (20 equiv) in the presence of [{Ir(OH)(cod)}$_2$] and dippbz in 1,4-dioxane at 70 °C for



Scheme 2. Deuterium-labeling experiments.

3 hours gave [D_3]**1a** containing deuterium at the methyl group (42% D).[17] ^{2}H NMR spectroscopic analysis of [D_3]**1a** clearly showed that the deuterium was incorporated only into the methyl group and the other possible reaction sites, such as the *ortho* positions of the two benzene rings, did not contain deuterium. In contrast, H–D exchange of **1v** was hardly observed, thus indicating that the secondary C–H activation does not occur under the present catalytic conditions (Scheme 2b).[18] The reaction of **1a** with deuterated alkene [D_3]**2a** at 70 °C for 2 hours gave **3aa** in 35% yield, and partial H–D exchange was observed at the three methylene groups of **3aa**, the methyl group of **1a**, and the vinyl group of alkene [D_3]**2a** (Scheme 2c). These results indicate that the C–H activation forming a hydridoiridium species and the alkene insertion are reversible.

The catalytic cycle proposed for the present hydroalkylation of the alkene **2** with **1a** is illustrated in Scheme 3. The



Scheme 3. Plausible catalytic cycle.

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reaction of **1a** with the hydroxoiridium **A** forms the amidoiridium **B** upon releasing H_2O. Directed C–H activation of the methyl C–H bond by iridium forms the alkyl(hydrido)iridium(III) species **C**. Linear-selective alkene insertion to the Ir–H bond forms **D**, and successive irreversible reductive elimination gives the amidoiridium **E**. Hydrolysis of **E** gives the addition product **3a** and regenerates **A**.

In summary, we have disclosed that direct alkylation of a methyl group of di- and trisubstituted ureas with terminal alkenes by C(sp^3)–H bond activation proceeded to give the corresponding addition products in high yields. The reaction was efficiently catalyzed by a hydroxoiridium/bisphosphine complex, which generates an amidoiridium intermediate by reaction with ureas having an N–H bond. The methyl group of the ureas were selectively alkylated with the terminal alkenes, thus giving the linear addition products. The present method provides easy access to biologically active compounds containing either an amino group or a urea moiety in an atom-economical manner.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenes · C–H activation · iridium · reaction mechanisms · synthetic methods

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Communications

C–H Activation

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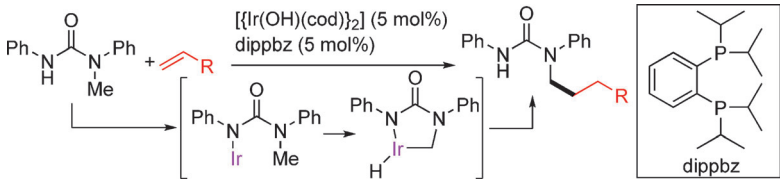
Hydroxoiridium-Catalyzed Hydroalkylation of Terminal Alkenes with Ureas by C(sp^3)–H Bond Activation



Direct alkylation of a methyl group, on di- and trisubstituted ureas, with terminal alkenes by C(sp^3)–H bond activation proceeded in the presence of a hydroxoiridium/bisphosphine catalyst to give high yields of the corresponding addition products. The hydroxoiridium/bisphosphine complex generates an amidoiridium intermediate by reaction with ureas having an N–H bond.

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