Organic LETTERS

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Unique Regioselectivity in the C(sp^3)−H α-Alkylation of Amines: The Benzoxazole Moiety as a Removable Directing Group

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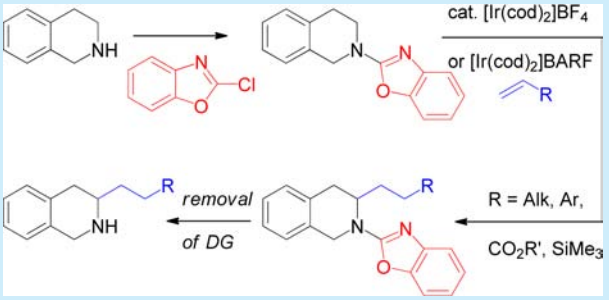
Supporting Information

ABSTRACT: The benzoxazol-2-yl- substituent was found to act as a removable activating and directing group in the Ir-catalyzed alkylation of C(sp^3)−H bonds adjacent to nitrogen in secondary amines. It can be easily introduced by oxidative coupling or by an S_NAr reaction, and it can be removed by hydroxide or by hydride reduction. For 1,2,3,4-tetrahydroisoquinolines, activation exclusively takes place in the 3-position. A variety of activated as well as unactivated terminal olefins are suitable reaction partners.



The regioselective manipulation of unactivated C−H bonds in organic molecules has attracted considerable attention in the past decade due to its high synthetic potential.[1] A possible solution for the position-selective discrimination of these ubiquitous functionalities is the use of directing groups which usually coordinate a transition metal capable of inserting into a neighboring C(sp^2)−H or C(sp^3)−H bond.[2] Clearly, removable directing groups are of higher synthetic value compared to substituents remaining in the molecule.[3] Since the pioneering studies of Murai on ruthenium-catalyzed α-alkylations of amines,[4] various directed activations of aliphatic C−H bonds adjacent to nitrogen use the 2-pyridyl group[5] which can be removed in a two-step protocol consisting of either catalytic hydrogenation or N-alkylation followed by hydride reduction.[6]

In the search for alternative directing groups which should ideally be removable in a single step, we chose 1,2,3,4-tetrahydroisoquinoline as a model substrate, as the activation of its 1-position provides access to various classes of alkaloids. Its transformation to 2-[(*E*)-phenyldiazenyl]-1,2,3,4-tetrahydroisoquinoline with benzenediazonium chloride[7] and subsequent reaction with ethyl acrylate in the presence of various Rh-[8] and Ir-sources[9] and ligands[10] exclusively resulted in single or double substitution of the *ortho* positions of the phenyl ring while reactions at sp^3-centers could not be observed. Blocking the reactive *ortho* positions with fluorine did not prove useful either. Moreover, the triazenes showed spontaneous autoxidation in the benzylic position under formation of hydroperoxides. The same phenomenon was observed with the popular *N*-(2-pyridyl) substituent.

The benzoxazol-2-yl (Bo-) group should provide similar chelation assistance[11] and can be introduced by metal-free oxidative coupling of the secondary amine with benzoxazole in the presence of Bu_4NI and *tert*-butylhydroperoxide.[12] Alternatively, the amine can be reacted with commercially available 2-chlorobenzoxazole in the presence of Hünig's base.[13] In most cases, the latter method provides superior yields. In contrast to the frequently used activating groups of the 2-pyridyl type,[14] the Bo-group can be efficiently removed in a single step using either KOH in ethylene glycol or $LiAlH_4$ (vide infra).

Interestingly, the benzoxazol-2-yl group provides an efficient and highly selective C(sp^3)−H activation in conjunction with $[Ir(cod)_2]BF_4$ or $[Ir(cod)_2]BARF$ [BARF = tetrakis(3,5-trifluoromethylphenyl)borate] as the catalyst and ethyl acrylate as the coupling partner. Surprisingly, the reaction occurs exclusively in the 3-position, whereas the activation of the methylene group in the 1-position which would benefit from insertion into the benzylic C−H bond is not observed. The latter selectivity has been observed, e.g. via photoredox catalysis,[15] oxidative Cu-catalysis,[16] oxidative Fe-catalysis,[17] or anodic oxidation[18] which all exhibit selectivity for the benzylic position (Scheme 1).

Nevertheless, formation of 1,3-disubstituted products could be detected when high catalyst loadings and long reaction times were applied. To draw a comparison between the benzoxazol-2-yl and the 2-pyridyl group, 2-(pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline was reacted with ethyl acrylate in the presence of Ir precursors under various conditions. In contrast to the Bo-derivative, the 2-pyridyl derivative showed very low conversion and no appreciable regioselectivity.

To explore the scope of the reaction, various olefins were reacted with compound **1** in the presence of 7 mol % of the iridium precursor, the results being summarized in Table 1.

The BARF counterion generally improved the reaction rate, but byproducts were observed in some cases. A ligand-free alkylation[19] of C(sp^2)−H bonds in 2-ferrocenylpyridine under similar conditions has been reported by the Shibata group.[20]

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Scheme 1. Examples for C−H Activation on 1,2,3,4-Tetrahydroisoquinolines

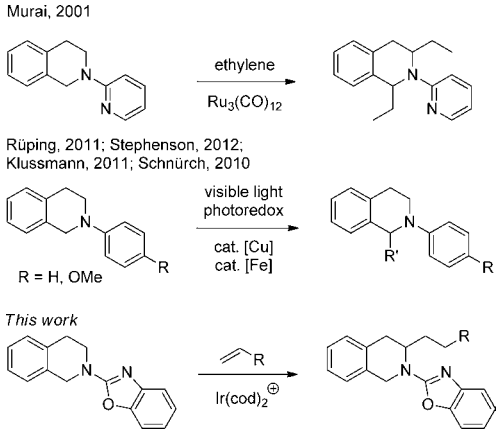
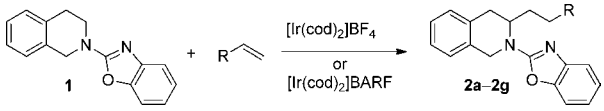


Table 1. Ir-Catalyzed Alkylation of Benzoxazole 1 with Various Olefins



entry	olefin	catalyst	product	yield (%)[a]
1	ethyl acrylate[c]	$[Ir(cod)_2]BF_4$	**2a**	84
2	methyl acrylate[c]	$[Ir(cod)_2]BF_4$	**2b**	78
3	styrene[b]	$[Ir(cod)_2]BARF$	**2c**	81[d]
4	vinylboronic acid pinacol ester[b]	$[Ir(cod)_2]BARF$	**2d**	61[d,e]
5	vinyltrimethylsilane[c]	$[Ir(cod)_2]BARF$	**2e**	41[d]
6	allylbenzene[b]	$[Ir(cod)_2]BARF$	**2f**	78
7	1-hexene[b]	$[Ir(cod)_2]BARF$	**2g**	83

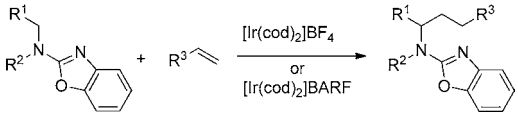
[a]Isolated yield after chromatography. [b]Conditions A: benzoxazole **1**, catalyst (7 mol %), olefin (8 equiv), DME (0.2 M), 140 °C, 1−2 h, microwave, 300 W. [c]Conditions B: benzoxazole **1**, catalyst (7 mol %), olefin (8 equiv), DME (0.2 M), 85 °C, 4−48 h. [d]Incomplete conversion. [e]Formation of 1,3-disubstituted product (not isolated).

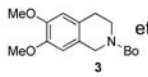
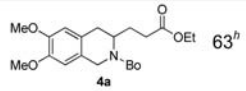
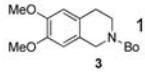
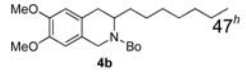
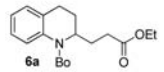
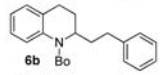
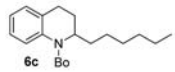
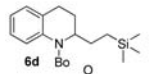
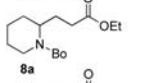
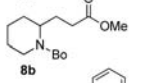
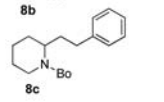
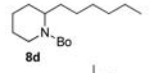
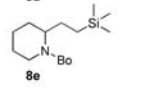
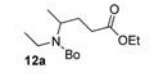
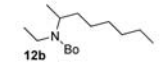
The same authors successfully employed a cationic Ir-(tolBINAP) complex for the asymmetric C(sp^3)−H bond activation in 2-(alkylamino)pyridines while the method was not extended to secondary amines.[21] In our case, however, the addition of racemic or enantiopure tolBINAP proved detrimental to the performance of the catalyst. The results of variation of the parent amine are summarized in Table 2.

While moderate to high yields and good selectivities for the monoalkylation were observed in the six-membered series, the activation of 2-(pyrrolidin-1-yl)benzoxazole (**9**) under identical conditions produced mixtures of mono- to trialkylated products. In contrast, the open-chain substrate **11** derived from diethylamine[22] gave a clean monoalkylation while its dimethyl analogue **10** produced no conversion instead. The reaction of substrate **1** with various alkynes (terminal and internal) showed low conversion.

The single step removal of the Bo-group can be effected by treatment with KOH in ethylene glycol at 140 °C or under reductive conditions with $LiAlH_4$ in refluxing THF (Scheme 2). In the case of ester **2a**, lactamization to 1,5,10,10a-tetrahydro-pyrrolo[1,2-*b*]isoquinolin-3(2*H*)-one (**15**) occurred. A higher reaction temperature was required for N-deprotection,

Table 2. Ir-Catalyzed α-Alkylation of Benzoxazol-2-ylamines



entry	parent amine	olefin	product	yield(%)[a]
1		ethyl acrylate[b,d]		63[h]
2		1-hexene[b,d]		47[h]
3		ethyl acrylate[b,d]		95
4		styrene[b,d]		73[h]
5		1-hexene[b,d]		66[h]
6		vinyltrimethyl-silane[b,d]		81
7		ethyl acrylate[b,e]		57[h,i]
8		methyl acrylate[b,e]		51[i]
9		styrene[b,d]		48[h,i]
10		1-hexene[b,d]		42[h,i]
11		vinyltrimethyl-silane[c,d]		39[h,i]
12		ethyl acrylate	[f]	–
13		ethyl acrylate	[g]	–
14		ethyl acrylate[c,d]		64[i]
15		1-hexene[b,d]		53[h,i]

Bo = Benzoxazol-2-yl. [a]Isolated yield after chromatography. [b]Conditions A: benzoxazole **1**, catalyst (7 mol %), olefin (8 equiv), DME (0.2 M), 140 °C, 1−2 h, microwave, 300 W. [c]Conditions B: benzoxazole **1**, catalyst (7 mol %), olefin (8 equiv), DME (0.2 M), 85 °C, 4−48 h. [d]$[Ir(cod)_2]BARF$ was used as the catalys. [e]$[Ir(cod)_2]BF_4$ was used as the catalyst. [f]Mixture of products, see text. [g]No conversion. [h]Incomplete conversion. [i]Formation of 1,3-disubstituted product (not isolated).

presumably due to charge repulsion between the nucleophile and the free carboxylate.

In summary, a novel removable directing group for the Ir-catalyzed alkylation of C(sp^3)−H bonds adjacent to nitrogen has been found. In tetrahydroisoquinolines, the benzoxazol-2-yl group provides unique regioselectivity complementary to existing methods of C−H activation.[23] The steric hindrance

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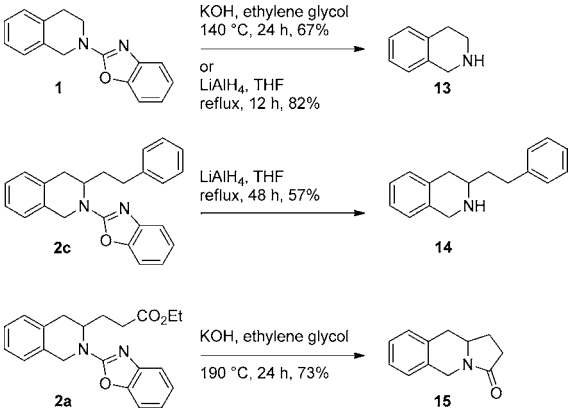
Scheme 2. Methods for Removal of the Benzoxazol-2-yl Group



imposed by the *peri*-hydrogen in position 8 in the intermediate Ir hydrido complex may account for the observed behavior although DFT calculations are not conclusive to date.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, ^{1}H, ^{13}C, and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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