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Ruthenium(II)-Catalyzed C(sp^3)–H α-Alkylation of Pyrrolidines

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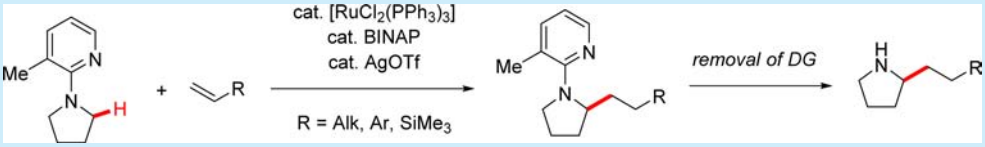
Supporting Information



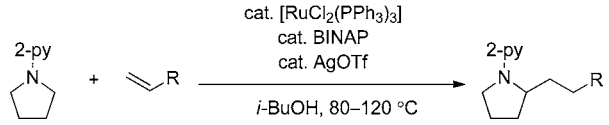
ABSTRACT: A catalytic system comprising $[RuCl_2(PPh_3)_3]$, AgOTf, and BINAP enabled atom- and step-economical additions of C(sp^3)–H bonds onto unactivated alkenes **2** under comparably mild reaction conditions. The pyridyl directing group was easily removed to furnish the corresponding (*NH*)-free amines with ample scope.

Catalyzed functionalizations of unactivated C–H bonds have in recent years emerged as powerful tools in organic synthesis.[1] Among these processes, metal-catalyzed additions of arenes onto C–C multiple bonds, hydroarylation reactions,[2] are particularly attractive due to the ideal atom economy.[3] Based on pioneering studies by Murai and co-workers,[4] ruthenium[5] catalysts were identified as arguably the most useful complexes for hydroarylations through activation of otherwise inert C–H bonds.[6] Thus far, the most active catalysts are based on $[RuH_2(CO)(PPh_3)_3]$, $[RuH_2(PPh_3)_4]$, $[Ru(CO)_2(PPh_3)_3]$, $[Ru_3(CO)_{12}]$, or $[RuH_2(H_2)_2(PCy_3)_2]$, which are unfortunately often rather unstable or relatively expensive. Significant practical progress in this area was achieved through the in situ formation of $[RuH_2(PPh_3)_4]$ from $[RuCl_2(p\text{-cymene})_2]$ and sodium formate.[7] Whereas this catalytic system showed high catalytic activity, it proved, as of yet, to be restricted to activated alkenes, that is vinyl silanes and styrenes. In contrast, we recently devised highly efficient ruthenium-catalyzed hydroarylations of unactivated alkenes employing various (hetero)arenes through carboxylate assistance.[8,9]

Unfortunately, catalytic alkylations involving the cleavage of C(sp^3)–H bonds[10] have thus far met with less success. For instance, despite the progress on the ruthenium-catalyzed C(sp^3)–H alkylations by Murai[11] and others,[12] these protocols were restricted to the use of $Ru_3(CO)_{12}$ as the catalyst under relatively harsh reaction conditions and with rather high catalyst loadings. Within our research program on step-economical ruthenium(II)-catalyzed C–H bond transformations,[13] we observed that the performance and chemoselectivity of directed C(sp^3)–H alkylations with unactivated alkenes on challenging pyrrolidines can be significantly improved when using $[RuCl_2(PPh_3)_3]$ as the catalyst. Hence, a catalytic system consisting of $[RuCl_2(PPh_3)_3]$, AgOTf, and BINAP allowed for efficient C(sp^3)–H activation under comparably mild reaction conditions (Scheme 1), the results of which we wish to disclose herein.

We initiated our studies by exploring representative ruthenium precursors and additives for the envisioned hydroalkylation of unactivated alkene **2a** (Table 1 and Table S-1 in the Supporting Information). Preliminary experiments revealed BINAP to be ideal among a variety of ligands. The C–H activation of pyrrolidine **1a** with the previously used $[Ru_3(CO)_{12}]$[11] as the catalyst gave only unsatisfactory conversion (entry 1). Notably, more promising results were achieved utilizing $[RuCl_2(p\text{-cymene})]_2$ (entry 2). A set of representative additives (KPF_6, NaOTf, AgOTf, AgOAc, $AgSbF_6$, or $AgBF_4$) were subsequently probed, and AgOTf was identified as being optimal (entries 3–7). Among different solvents, the most efficient catalysis was accomplished in protic reaction media (entries 8–12), with *i*-BuOH being ideal. To our delight, utilizing the catalyst $[RuCl_2(PPh_3)_3]$ proved beneficial, thus furnishing the desired monoalkylated product **3aa** in high yields (entries 13–16). Test reactions clearly illustrated the importance of $[RuCl_2(PPh_3)_3]$ as well as BINAP (entries 17–20).

Scheme 1. Ruthenium-Catalyzed C(sp^3)–H Hydroalkylation of Alkenes



With a highly selective catalytic system in hand (Table 1, entry 16), we examined the influence exerted by substituents at the heteroaromatic moiety (Scheme 2). Thus, the optimized ruthenium catalyst proved applicable to high-yielding transformations of pyrrolidines with 3-, 4-, or 5-substitutents on the pyridyl group, thereby selectively delivering the alkylated products **3ba**–**3ha**. Notably, the optimized catalyst was not limited to pyridine derivatives, but enabled the C–H activation using isoquinolines (**3ia**) as well. Contrarily, methyl groups either on the pyridine (**1j**) or on the pyrrolidine (**1k**) had a detrimental effect.

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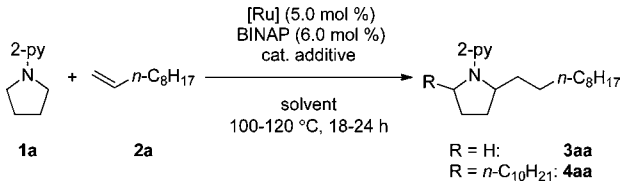
Table 1. Optimization of the C(sp^3)−H Alkylation[a]

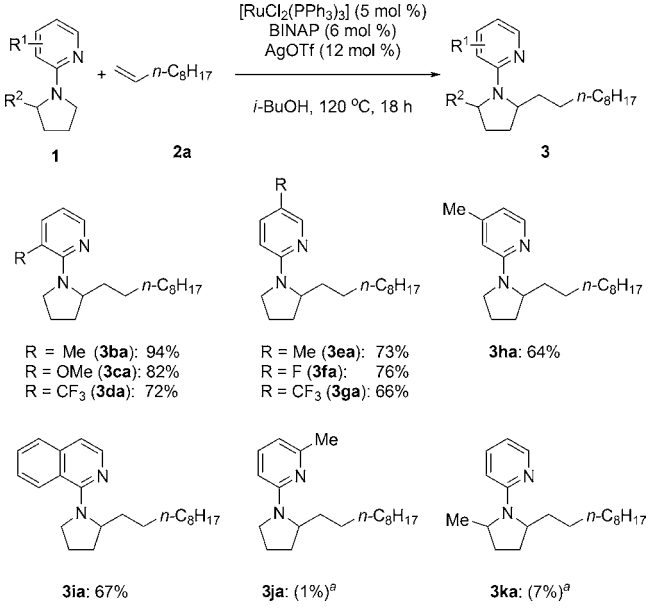


1a 2a

entry	[Ru] complex	additive (mol %)	solvent	3aa
1	$[Ru_3(CO)_{12}]$	–	*i*-PrOH	14%
2	$[RuCl_2(p\text{-cymene})]_2$	–	*i*-PrOH	17%
3	$[RuCl_2(p\text{-cymene})]_2$	AgOAc (30)	*i*-PrOH	23%
4	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$ (30)	*i*-PrOH	38%
5	$[RuCl_2(p\text{-cymene})]_2$	$AgBF_4$ (30)	*i*-PrOH	29%
6	$[RuCl_2(p\text{-cymene})]_2$	KPF_6 (30)	*i*-PrOH	44%
7	$[RuCl_2(p\text{-cymene})]_2$	AgOTf (30)	*i*-PrOH	39%
8	$[RuCl_2(p\text{-cymene})]_2$	AgOTf (30)	DCE	50%
9	$[RuCl_2(p\text{-cymene})]_2$	AgOTf (30)	NMP	54%
10	$[RuCl_2(p\text{-cymene})]_2$	AgOTf (30)	1-BuOH	79% (50%)
11	$[RuCl_2(p\text{-cymene})]_2$	AgOTf (30)	2-BuOH	66% (32%)
12	$[RuCl_2(p\text{-cymene})]_2$	AgOTf (30)	*i*-BuOH	81% (48%)
13	$[RuCl_2(p\text{-cymene})]_2$	AgOTf (6)	1-BuOH	51% (41%)
14	$[RuCl_2(PPh_3)_3]$	AgOTf (6)	1-BuOH	64% (51%)
15	$[RuCl_2(PPh_3)_3]$	NaOTf (12)	*i*-BuOH	80% (70%)
16	**$[RuCl_2(PPh_3)_3]$**	**AgOTf (12)**	***i*-BuOH**	**84% (73%)**
17	–	AgOTf (12)	*i*-BuOH	0
18	$[RuCl_2(PPh_3)_3]$	–	*i*-BuOH	4%[b]
19	$[RuCl_2(PPh_3)_3]$	–	*i*-BuOH	8%
20	$[RuCl_2(PPh_3)_3]$	AgOTf (12)	*i*-BuOH	<1%[b]

[a]Reaction conditions: entries 1−12: **1a**/**2a** = 1:2, entries 13−14: **1a**/**2a** = 1:1.1, entries 15−21: **1a**/**2a** = 3:1, [Ru] complex (5.0 mol %), BINAP (6.0 mol %), additive (6.0−30 mol %), 100−120 °C; GC analysis with *n*-tridecane as the internal standard; isolated yields in parentheses; entries 3−14: **4aa** was obtained in 4−22% conversions. [b]Without BINAP.

Scheme 2. C(sp^3)−H Alkylation with Pyrrolidines 1

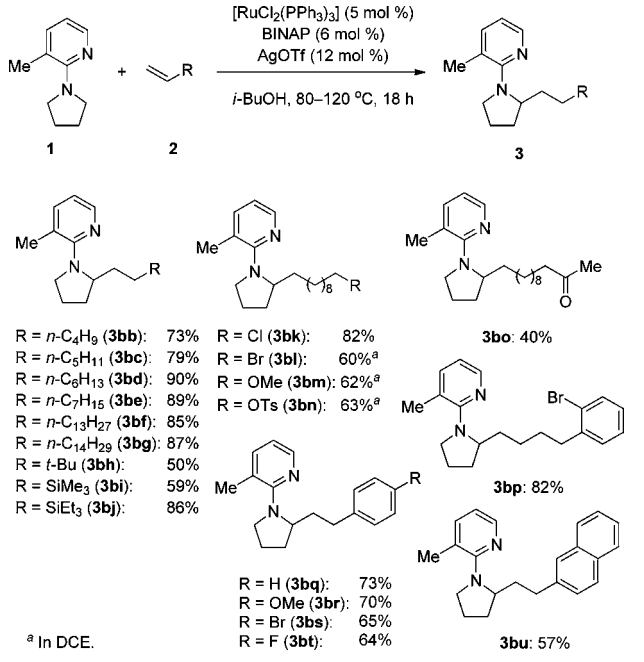


1 2a 3

[a]GC analysis with *n*-tridecane as the internal standard.

Thereafter, we explored the versatility of the optimized system by testing a representative set of unactivated alkenes **2** (Scheme 3). Different substrates **2b−h** furnished the corresponding products **3bb−3bh** in high yields even at a

Scheme 3. Ruthenium(II)-Catalyzed C(sp^3)−H Alkylation with Alkene 2



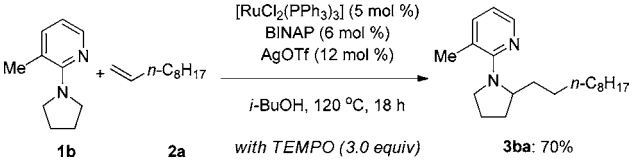
[a] In DCE.

significantly reduced reaction temperature of 80 °C. Notably, the catalytic system tolerated valuable functional groups, such as silanes (**2i** and **2j**) or enolizable ketones (**2o**). Intriguingly, competition experiments with haloalkenes **2k** and **2l** highlighted the excellent chemoselectivity of the C(sp^3)−H alkylations, in that products stemming from direct C−H bond alkylations with alkyl halides were not detected.[14] Moreover, hydroalkylations with substrates **2l−2n** proceeded as well, albeit with the formation of significant amounts of products stemming from nucleophilic substitution. Fortunately, improved results were obtained when using aprotic DCE as the solvent. Likewise, styrene derivatives **2q−2u** proved to be appropriate substrates, thereby delivering the corresponding alkylated products **3bq−3bu**.

Given the unique reactivity profile of the novel ruthenium catalyst, we subsequently performed mechanistic studies to rationalize its mode of action. Thus, SET-type processes appeared less likely to be operative, as indicated by successful C(sp^3)−H alkylations in the presence of stoichiometric amounts of the radical scavenger TEMPO (Scheme 4).

Furthermore, ruthenium-catalyzed C(sp^3)−H alkylations with $[D]_4$-MeOH as the solvent indicated the C−H bond metalation to be reversible in nature (Scheme 5). Notably, the treatment of **1b** with the optimized catalytic system in $[D]_4$-

Scheme 4. Mechanistic Studies in the Presence of TEMPO



1b 2a

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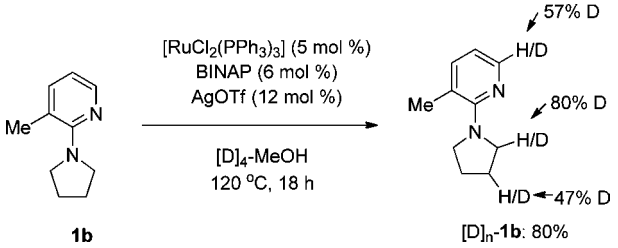
MeOH also showed significant deuterium incorporation at the β-positions[11] of substrate **1b**.

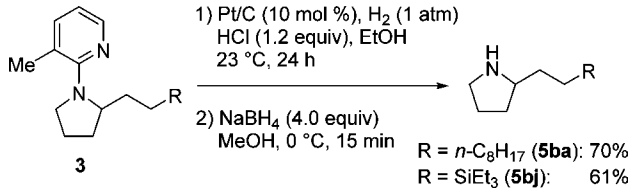
Scheme 5. Studies with Isotopically Labeled Solvents



1b [D]$_n$-**1b**: 80%

Finally, we were pleased to find that the pyridyl directing group was efficiently removed. Thus, a hydrogenation−hydride reduction protocol[15] was successfully applied to substrates **3**, providing access to the desired (*NH*)-free pyrrolidines **5ba** and **5bj** under mild reaction conditions (Scheme 6).

Scheme 6. Removal of the Directing Groups



3 R = *n*-C_8H_{17} (**5ba**): 70%
R = $SiEt_3$ (**5bj**): 61%

In summary, we have reported on novel ruthenium(II)-catalyzed C(sp^3)−H alkylations with various alkenes employing pyrrolidines[16] with a removable directing group. The ruthenium system comprised of [$RuCl_2(PPh_3)_3$], AgOTf, and BINAP enabled step-economical additions of C(sp^3)−H bonds onto unactivated alkenes with ample scope under mild reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. 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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(16) The hydroarylation of 1-decene with *N*-pyrid-2-yl piperidine gave 41% of the desired monoalkylated product under otherwise identical reaction conditions.

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