Synthetic Methods

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Base-Controlled Completely Selective Linear or Branched Rhodium-(I)-Catalyzed C–H *ortho*-Alkylation of Azines without Preactivation

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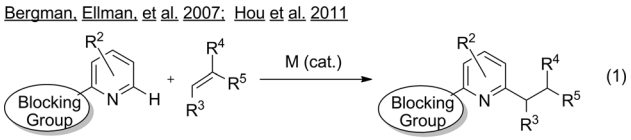
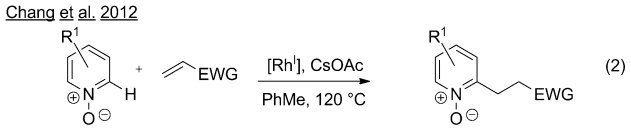
Abstract: *A [Rh^{I}]/bisphosphine/base catalytic system for the ortho-selective C–H alkylation of azines by acrylates and acrylamides is reported. This catalytic system features an unprecedented complete linear or branched selectivity that is solely dependent on the catalytic base that is used. Complete branched selectivity is even achieved for ethyl methacrylate, which enables the introduction of a quaternary carbon center. Excellent functional group compatibility is demonstrated for both linear and branched alkylations. The operational simplicity and broad scope of this transformation allow for rapid access to functionalized azines of direct pharmaceutical and agrochemical relevance.*

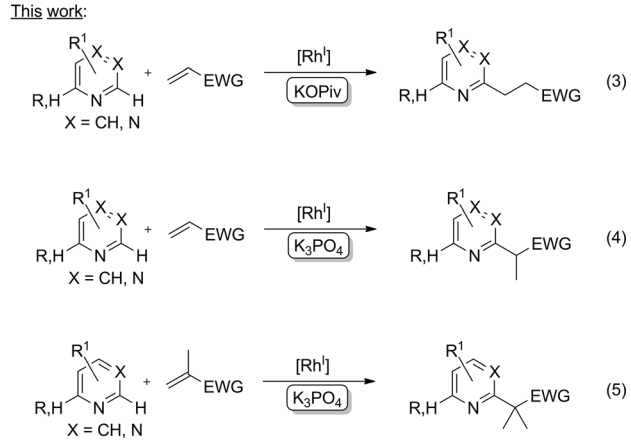
Heterocycles are found in more than 90% of the new synthetic biologically active molecules reported in the literature.[1] The azine family, which includes pyridines, pyrimidines, pyridazines and pyrazines, is one of the most extensively used subclasses of heterocycles in the pharmaceutical and agrochemical industry, and considerable efforts have been dedicated to their synthesis and functionalization.[2] In particular, the ability to directly access carboxylic acid derivatives from unsubstituted heteroarenes would present an exciting opportunity for achieving hepatoselective delivery of drug-like molecules via organic-anion transporting polypeptides (OATPs)—a strategy for the hepatic uptake of drugs that has been well validated.[3]

The direct regioselective C–H functionalization of unsubstituted azines would represent a highly efficient method for incorporating carboxylic acid functionality.[4,5] However, few methods are available for the *ortho*-selective C–H alkylation of azines. The seminal example made use of a [Rh^{I}]/PCy$_3$/HCl catalytic system for the *ortho* alkylation of pyridines and quinolines by C–H bond addition to unactivated alkenes [Eq. (1)].[6] Although efficient alkylation occurred for pyridines substituted with a steric blocking group at an *ortho* position, no alkylation was observed for pyridines lacking this substituent, presumably due to strong [Rh^{I}] coordination of the unsubstituted pyridine. Subsequently, Hou et al. reported the rare earth-catalyzed *ortho* alkylation of similar heterocycles with unactivated alkenes [Eq. (1)].[7] This reaction was also efficient for azines bearing an *ortho* steric blocking group, but the absence of this substituent resulted in catalyst poisoning. Finally, Chang described a [Rh^{I}]/dppe/CsOAc catalytic system, but alkylation was only reported for azines preactivated as *N*-oxides [Eq. (2)].[8,9]





Herein, we report that unactivated azines with or without an *ortho* blocking group can be efficiently alkylated with α,β-unsaturated carboxylic acid derivatives using a [Rh^{I}]/bisphosphine catalytic system [Eq. (3)–(5)]. In an unprecedented finding, complete selectivity for either the linear [Eq. (3)] or branched [Eq. (4)] product can be achieved solely depending on the catalytic base that is used. The branched conditions can even be employed with methacrylates to provide the first examples of azine C–H alkylation with a Michael acceptor to introduce a quaternary center [Eq. (5)].



After intensive optimization, alkylation of 3-trifluoromethylpyridine in 76% yield was achieved with ethyl acrylate in the presence of [Rh(cod)Cl]$_2$, dppe, and potassium pivalate

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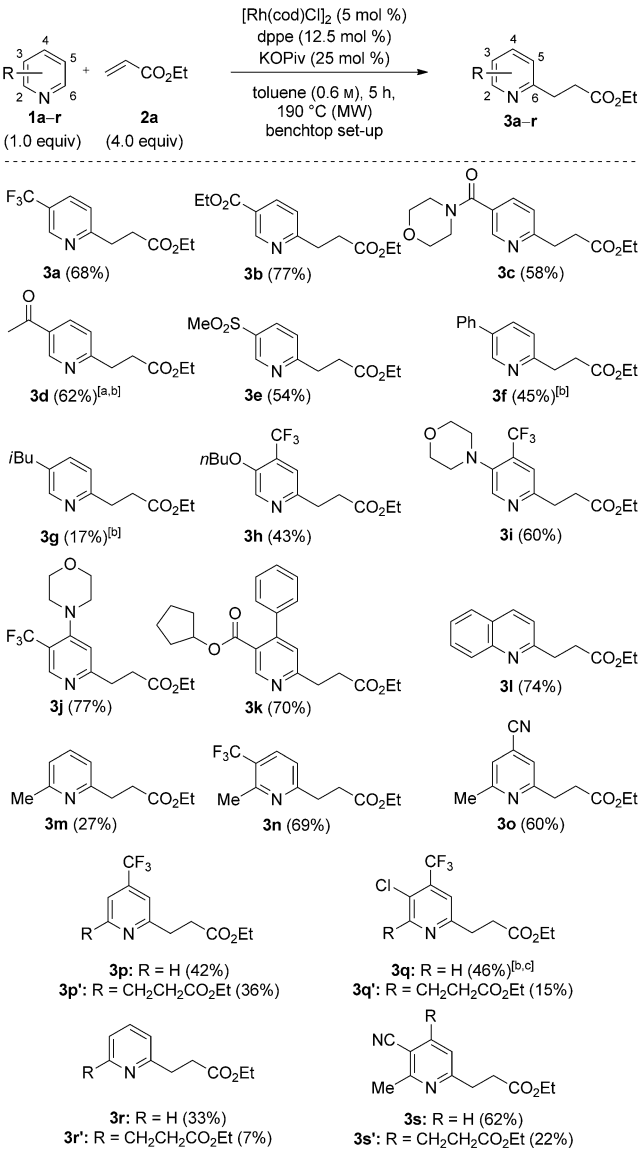


Scheme 1. Substrate scope for linear C–H alkylation of pyridines. [a] 160 °C instead of 190 °C. [b] 10 h reaction time instead of 5 h. [c] 120 °C instead of 190 °C.

(KOPiv) with microwave heating at 190 °C in toluene for 5 h (**3a**, Scheme 1). Significantly, the reaction proceeded with complete selectivity for linear mono-alkylation at the C6-position. KOPiv proved superior to all other bases, including CsOAc initially used by Chang, which gave a 22 % yield (see Table S1).[9] The stability of the $[Rh(cod)Cl]_2$ pre-catalyst to air and the low hygroscopicity of the KOPiv base enabled the reaction to be readily set up on the bench-top.

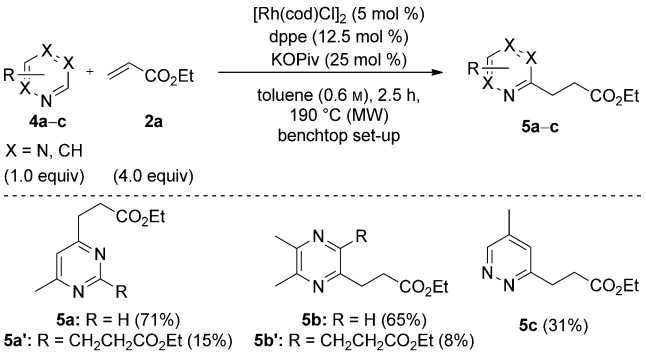
Broad scope for this reaction was observed for the pyridine coupling partner (Scheme 1). Carbonyl-containing functional groups, such as an ester (**3b**) or an amide (**3c**) led to the desired products in good to excellent yields. On the other hand, significant amounts of by-products were formed at 190 °C when 3-acetylpyridine was used, presumably due to enolate-mediated side reactions. This could be avoided by reducing the reaction temperature to 160 °C (**3d**). Other electron-withdrawing functional groups such as sulfone (**3e**) or phenyl (**3f**) were also compatible. With an electron-donating group such as isobutyl (**3g**) the reaction was significantly slower, but some product could be obtained when the reaction time was extended to 10 h. Notably, pyridines combining both an electron-donating and an electron-withdrawing group did not require more forcing conditions, and good to excellent yields were obtained regardless of the substitution pattern (**3h–k**).

The presence of a substituent at the C2-position of the pyridine ring, such as in quinoline, did not hamper the reaction with product **3l** obtained in 74 % yield. While 2-picoline gave 27 % yield (**3m**), significant improvement was obtained when adjoining an electron-withdrawing group to the ring (**3n**,**o**).

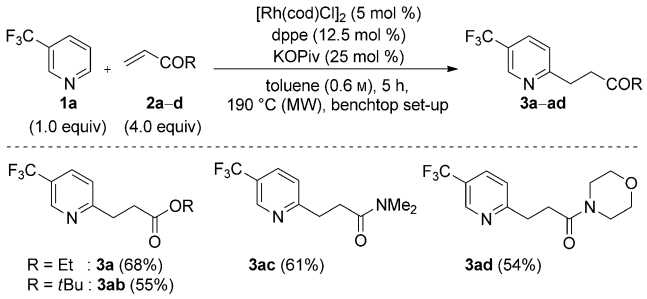
All of the previous reactions featured complete selectivity for mono-alkylation. However, when pyridine was substituted with a trifluoromethyl group at the *para*-position, the mono-alkylated product **3p** was obtained in 42 % yield along with the dialkylation product **3p′** in 36 % yield. Better selectivity was observed for 3-chloro-4-trifluoromethylpyridine (**3q**) when milder conditions were used (120 °C, 10 h). Parent pyridine also provided good selectivity in favor of the mono-alkylated product (**3r**), although with a modest yield. For 2-methylnicotinonitrile, the C2-alkylated product **3s** was obtained in 62 % yield along with the C3,C6-dialkylated product **3s′** in 22 % yield. This was the only example where alkylation did not occur solely at the position *ortho* to the pyridine nitrogen.

We next evaluated diazines, which are also highly represented in biologically active compounds.[1] Diazines were sufficiently reactive that the reaction time was decreased to minimize over-alkylation (Scheme 2). Complete regioselectivity in favor of the C6-position was observed with 4-methylpyrimidine, though a small amount of C2,C6-dialkylated product **5a′** was also obtained. A good yield of monoalkylated **5b** was also obtained from 2,3-dimethylpyrazine, again with a small amount of dialkylated product **5b′**. In contrast, 4-methylpyridazine led to significant amounts of by-products and the desired monoalkylated product **5c** was obtained in 31 % yield.

In addition to ethyl acrylate, other acrylate derivatives such as *tert*-butyl acrylate, **2b**, and *N*,*N*-dimethylacrylamide, **2c**, were suitable alkene partners (Scheme 3). Significantly, 4-



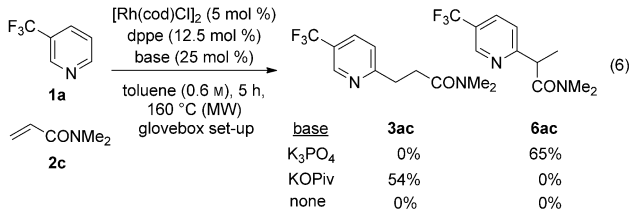
Scheme 2. Substrate scope for linear C–H alkylation of diazines.



Scheme 3. Evaluation of acrylate esters and amides.

acryloylmorpholine, **2d**, led to acceptable yields of the alkylated pyridine **3ad**, which can potentially be converted to a wide range of ketones by reaction with the corresponding organometallic reagents.[10]

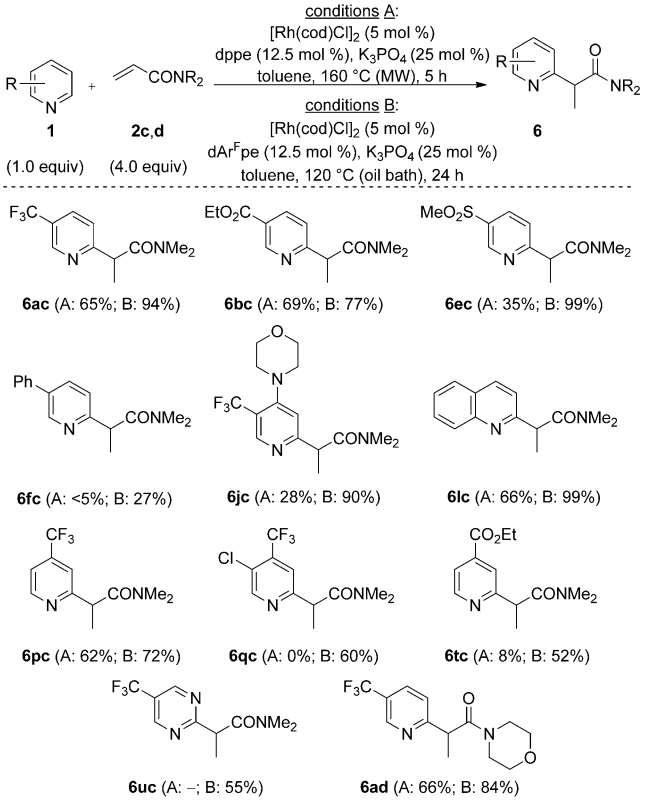
All of the reactions presented in this study so far feature complete linear selectivity as assessed by ^{1}H NMR of the crude reaction mixtures, consistent with virtually all of the intermolecular C–H bond additions to Michael acceptors whether catalyzed by [Co], [Ir], [Ru], [Rh], or [Pd].[5,11,12] It was therefore exciting for us to discover that the alkylation of 3-trifluoromethylpyridine, **1a**, by acrylamide **2c** led to a good yield of product **6ac** through the use of a $[Rh(cod)Cl]_2$/dppe catalyst system with K_3PO_4 as the catalytic base instead of KOPiv [Eq. (6)].[13] In contrast, the linear product **3ac** was the



sole alkylation product of the reaction when KOPiv was used as base under otherwise identical conditions. Such a switch in regioselectivity in metal-catalyzed hydroarylation of alkenes is unprecedented, not only due to the very simple change in reaction conditions under which it is operated (K_3PO_4 vs. KOPiv), but also due to its complete selectivity.

Satisfying yields of branched product **6ac** could be obtained using the $[Rh(cod)Cl]_2$/dppe/K_3PO_4 catalytic system depicted in Equation (6), but some limitations in the scope were observed after further investigation (vide infra). A second screening campaign established that replacing dppe with its electron-deficient analog d(3,5-$(CF_3)_2$Ph)pe (dAr^Fpe) resulted in a significant increase in yield (see Table S2). With this more efficient catalyst system, the reaction temperature could be lowered to 120 °C. The nature of the base was still crucial for branched/linear selectivity and reaction efficiency, as the use of KOPiv as well as a number of other bases instead of K_3PO_4 resulted in only trace amounts of the linear product (see Table S2).

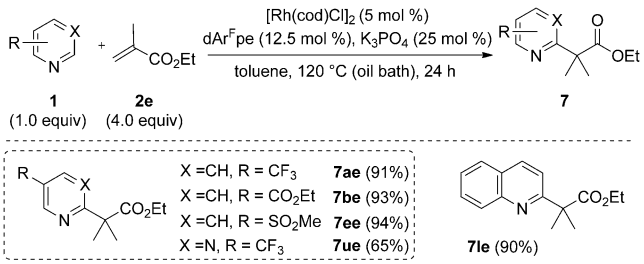
We evaluated the scope of the reaction under conditions **A**, with a $[Rh(cod)Cl]_2$/dppe/K_3PO_4 catalytic system at 160 °C,



Scheme 4. Substrate scope for branched C–H alkylation using acrylamides.

and conditions **B** with dAr^Fpe instead of dppe at 120 °C (Scheme 4). Very good scope with complete retention of the branched selectivity was observed for both of these conditions, though the broadest scope was achieved for conditions **B**. Alkylations of 3-trifluoromethylpyridine (**6ac**), ethyl nicotinate (**6bc**), quinoline (**6lc**) and 4-trifluoromethylpyridine (**6pc**) by acrylamide **2c** were accomplished in good yields with conditions **A**, and in excellent to quantitative yields with conditions **B**. Even when modest yields are obtained with conditions **A**, as with 3-methylsulfonylpyridine (**6ec**) or 3-trifluoromethyl-4-morpholinepyridine (**6jc**), almost quantitative yields are obtained with conditions **B**. The superiority of conditions **B** over conditions **A** was also apparent when 3-phenylpyridine (**6fc**), 3-chloro,4-trifluoromethylpyridine (**6qc**) or ethyl isonicotinate (**6tc**) were used. While only traces of the desired products could be observed with conditions **A**, moderate to good yields could be obtained with conditions **B**. Finally, the alkylation of 3-trifluoromethylpyridine by 4-acryloylmorpholine also led to a good to excellent yield of the corresponding branched product (**6ad**) with both conditions.

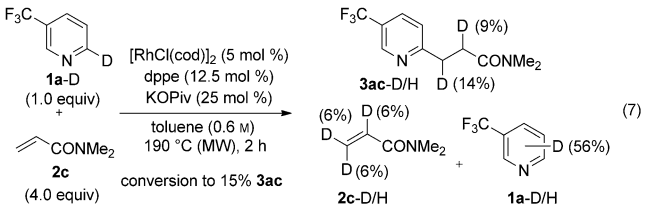
Methacrylate derivatives were also explored for the direct incorporation of quaternary centers. While *N*,*N*-dimethyl methacrylamide was insufficiently reactive and did not couple, ethyl methacrylate, **2e**, was a highly effective substrate for branched alkylation, leading to azines **7ae**, **7be** and **7ee**, diazine **7ue** and quinoline **7le** in excellent yields (Scheme 5). These are the first examples of azine C–H

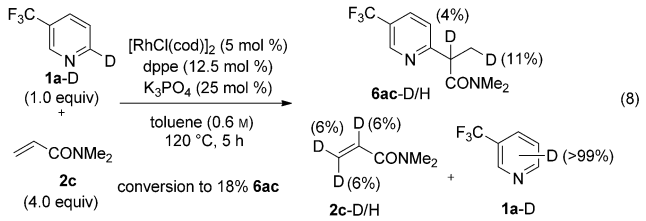


Scheme 5. Branched C–H alkylation using ethyl methacrylate.

alkylation with a Michael acceptor to introduce a quaternary center.

To probe mechanistic differences between the KOPiv-catalyzed linear and K_3PO_4-catalyzed branched alkylations, 2-deutero-5-trifluoromethylpyridine, **1a**-D, was reacted with





acrylamide **2c** using both the linear and branched protocols and halted at early conversion [Eqs. (7) and (8)]. C–H activation under the linear conditions is highly reversible as evidenced by significant H/D scrambling of **1a**-D [Eq. (7)]. In contrast, C–H activation for the branched conditions is irreversible as evidenced by the complete absence of H/D scrambling of **1a**-D [Eq. (7)]. The lack of deuterium exchange for branched alkylation of **1a**-D, enabled initial rates to be determined for protio and deuterio **1a** under the branched alkylation conditions (see Scheme S1). A modest kinetic isotope effect (KIE) of 1.34 was observed.

Under both linear and branched reaction conditions [Eqs. (7) and (8)], deuterium incorporation was observed not only at both the α and the β alkyl sites in products **3ac**-D/H and **6ac**-D/H, but also at the α and β vinyl sites in the recovered acrylamide **2c**. Deuterium incorporation in the products and in acrylamide **2c** could occur by Rh^I-catalyzed oxidative addition of the azine C–H bond followed by reversible Rh^{III}-hydride migratory insertion of acrylamide **2c**. This pathway is consistent with well-documented highly reversible migratory insertions for Rh-hydrides.[14,15]

A number of Rh-catalyzed C–C bond cleavage reactions have recently been reported.[16] It is therefore conceivable that deuterium could be incorporated into acrylamide **2c** and the linear and branched products **3ac** and **6ac** by reversible C–C bond formation. However, this pathway was ruled out by the complete lack of crossover upon submitting linear product **3ac** to the branched alkylation conditions and branched product **6ac** to the linear alkylation conditions (see Scheme S2). A detailed discussion is provided in the Supporting Information for possible mechanistic scenarios that explain the complete turnover in selectivity under the linear and branched reaction conditions.

In summary, we have developed a [Rh^I]-catalyzed *ortho*-selective alkylation of azines with acrylates and acrylamides with complete linear or branched selectivity controlled exclusively by catalytic base. This transformation has excellent functional group tolerance and is operationally simple thereby making it useful for drug discovery applications. The base-controlled switch in linear/branched selectivity is completely unprecedented and may be symptomatic of a novel mode of reactivity in [Rh^I]-catalytic systems. Further studies on extending the reaction scope to broader classes of nitrogen heterocycles and to asymmetric transformations is underway in our laboratories.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H activation · homogeneous catalysis · nitrogen heterocycles · regioselectivity

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Communications

Synthetic Methods

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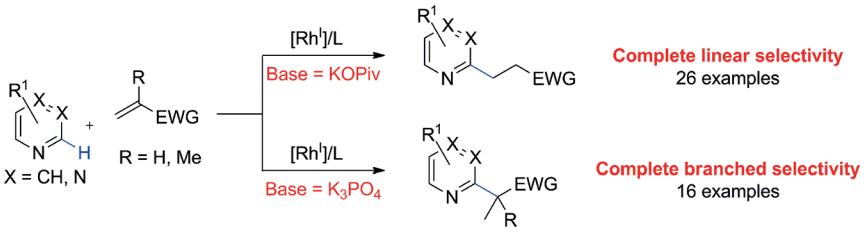
Base-Controlled Completely Selective Linear or Branched Rhodium(I)-Catalyzed C–H *ortho*-Alkylation of Azines without Preactivation



A basic choice: The linear/branched selectivity of an *ortho*-selective C–H alkylation of azines without preactivation is completely controlled by a simple switch between base catalysts. Under the "branched" conditions even quaternary carbon centers can be introduced. Excellent functional group compatibility is demonstrated for both linear and branched alkylations with acrylate derivatives.

