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Directed Ruthenium-Catalyzed C(sp^3)–H α-Alkylation of Cyclic Amines Using Dioxolane-Protected Alkenones

Artem A. Kulago,[a] Ben F. Van Steijvoort,[a] Emily A. Mitchell,[a] Lieven Meerpoel,[b] and Bert U. W. Maes[a,*]

[a] Organic Synthesis, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp, Belgium
Fax: (+32)-32-653-233; phone: (+32)-32-653-205; e-mail: bert.maes@uantwerpen.be
[b] Janssen Research & Development, a division of Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340, Beerse, Belgium

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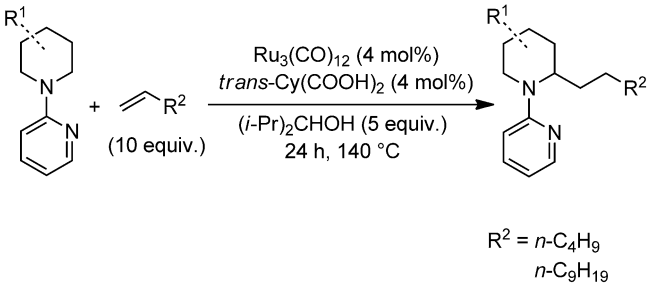
Abstract: A catalytic system for ruthenium-catalyzed C(sp^3)–H α-alkylation of piperidines with dioxolane-protected alkenones is reported. Dioxolane protection of the ketone proved crucial to obtain alkylation products. A diverse set of highly substituted piperidines was readily prepared in moderate to good yields *via* this methodology from easily accessible starting materials (C-2, C-3 and C-4 substituted piperidines). When the methodology is applied to C-3 substituted piperidines, featuring two α positions, only monoalkylated products (2,5-disubstituted) are observed. Even bicyclic amines, which feature a fused piperidine moiety, can be used. The successful directing group as well as protecting group (ketal) removal is also demonstrated. The methodology thus allows one to further derivatize and access hitherto unknown functionalized cyclic amine derivatives and will be useful in molecular library synthesis.

Keywords: alkenes; C(sp^3)–H activation; directing groups; piperidines; ruthenium catalysis

Introduction

C-2 substituted saturated cyclic amines constitute an important and valuable skeletal core in a number of pharmaceuticals and natural products.[1] A variety of methodologies exists to synthesize these products directly from the corresponding cyclic amines.[2a,b] The vast majority of these methods involve the use of stoichiometric quantities of an activating reagent; a strong base (α-anion intermediate) or an oxidant (α-cation or α-radical intermediate).[2b] To address this disadvantage, a transition metal catalyst can alternatively be used to activate the α-position of cyclic amines.[3,4] However, the application of transition metal catalysis in this area still remains limited.[3,4] A key feature of this approach is the use of an N-bound directing group. A pyridin-2-yl group has been identified as a stable and efficient directing group for the direct catalytic C-2 functionalization of cyclic amines.[3b–d,g–j] It is simple to install (S_NAr or Pd catalysis)[5] and our laboratory has recently demonstrated that it can be easily removed after the α-functionalization process.[6] Within the saturated cyclic amines, pyrrolidines are far better explored for direct transition metal-catalyzed functionalization than piperidines. This is not surprising when one considers the inherently lower reactivity of six-membered rings *versus* their five-membered counterparts.[7] In the past years, our laboratory has developed a direct Ru-catalyzed C–H activation[8] protocol for the C-2 arylation[3g,i] and alkylation[3h] of substituted piperidines. The protocols have proved to be general, as justified by their applicability to other cyclic amine substrates. In 2012, we reported a C-2 alkylation strategy using 1-hexene and 1-undecene as model reagents (Scheme 1).[3h]

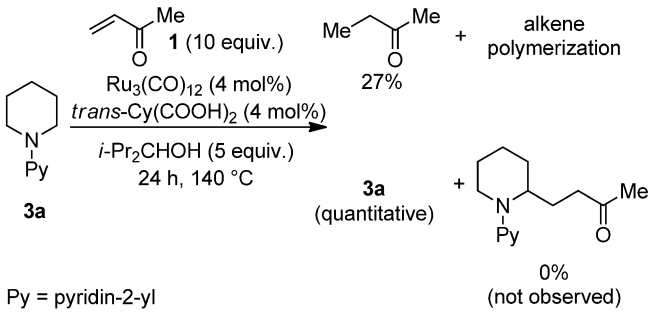


Scheme 1. Direct α-alkylation of piperidines using unfunctionalized alkenes.[3h]

Several challenges are associated with the use of 1-alkenes for this direct alkylation process. Under the applied reaction conditions, terminal alkenes can polymerize and/or isomerize to non-terminal alkenes. These internal alkenes are more stable than the 1-alkenes and need to isomerize back to the terminal position before direct functionalization can occur. In addition, direct alkylation is accompanied by a competitive reduction reaction of the alkene.[3h] It was found that the rate of direct functionalization *versus* reduction could be increased by the use of a sterically hindered alcohol (2,4-dimethyl-3-pentanol) and the addition of catalytic acid [*trans*-1,2-Cy(COOH)$_2$]. These findings were crucial to deliver a synthetically applicable direct alkylation process for the less reactive piperidine system. Up to now, only unfunctionalized alkenes have been applied using this protocol, so we wondered if the process would be compatible with oxygen functionalization in the alkene. If applicable, our expanded methodology would allow one to access piperidines with valuable functionality in the alkyl side-chain. In this manuscript, we report our findings on the introduction of 3-oxoalkyl moieties α to the nitrogen in piperidines and related cyclic amines using Ru catalysis.

Results and Discussion

The reaction conditions disclosed previously for the direct hexylation of piperidines with 1-hexene (Scheme 1) were chosen as a starting point for alkylation using piperidine **3a** as a model substrate. The use of methyl vinyl ketone (**1**) as an alkylating reagent was unfortunately not successful under these conditions and substrate **3a** was quantitatively recovered (Scheme 2). Interestingly, GC-MS analysis also indicated that alkene **1** was completely consumed, resulting in 2-butanone (27%) and polymerized products. We then envisaged a new strategy for successful alkylation based on ketone protection as a ketal (dioxolane) (Figure 1). Ultimately, cleavage of this dioxolane moiety after functionalization also allows one to



Scheme 2. Attempted direct α-alkylation of 1-pyridin-2-ylpiperidine (**3a**) with methyl vinyl ketone (**1**).[9]

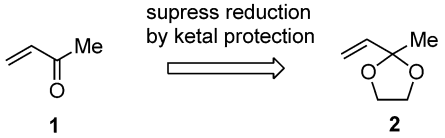
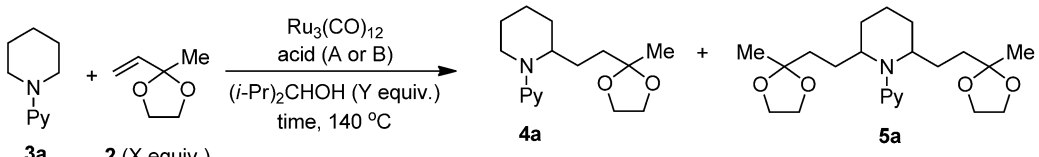


Figure 1. Design of the alkene.

access the desired keto functionality. Ketal-protected methyl vinyl ketone, (2-methyl-2-vinyl-1,3-dioxolane, **2**), under otherwise similar reaction conditions yielded 21% conversion of **3a** (Table 1, entry 2). Changing the acid from *trans*-1,2-cyclohexanedicarboxylic acid [*trans*-Cy(COOH)$_2$, "A"] to 3,4,5-trifluorobenzoic acid (TFBA, "B"), resulted in a slight increase in conversion (entry 3). These data indicate that alkene **2** possesses a much lower reactivity in comparison to the previously reported 1-hexene.[10] Notably, as observed with our C-2 hexylation protocol, the presence of catalytic acid is important, as it suppresses the reduction of alkene (entries 1–3). Subsequently, the effect of the quantities of both alkene and alcohol were investigated. For these experiments, dodecane was added as a co-solvent in order to compensate for differences in the reaction volume upon varying the loadings of these reagents. The increase in the concentration of 2,4-dimethyl-3-pentanol from 10 equiv. to 15 equiv., and from 10 equiv. to 40 equiv., showed a pronounced increase in the conversion of **3a** from 29% (entry 4) to 42% and 54%, respectively (entries 5 and 6). Doubling the concentration of alkene **2** from 10 equiv. to 20 equiv. further increased the conversion to 69% (entries 6 and 9). Additionally, it was noted that a high concentration of 2,4-dimethyl-3-pentanol is crucial to obtain higher conversions of **3a** when using this alkene loading (entries 7–9). Increasing the TFBA/$Ru_3(CO)_{12}$ loading to 8:8 mol% further improved the conversion of **3a** to 83% (entries 10 and 11). The effect of the ratio of the loading of the TFBA with respect to $Ru_3(CO)_{12}$ was also investigated (entries 11–14). The smallest quantity of unreacted starting material **3a** (8%) was observed when using 7 mol% TFBA and 8 mol% Ru_3CO_{12} (entry 13). In this instance, however, GC-MS data indicated the presence of side products, giving a mass balance (sum of **3a**, **4a** and **5a**) of only 81%. Shortening of the reaction time from 24 to 17 h allowed for the suppression of side product formation, as is reflected in the improved mass balance, as well as in the isolated yields of the reaction products (entry 15). At this stage, the re-screening of *trans*-Cy(COOH)$_2$ as acid additive reconfirmed that TFBA is superior as acid co-catalyst (90% *vs.* 75% conversion of **3a**, entries 15 and 16). When no acid was used, after 17 h only 40% of **3a** was converted to products and only reduced **2** was observed (entry 17). Even after 8 h reaction time, 76% of the alkene was already reduced (entry 18). These experiments clarify

Table 1. Optimization of the direct Ru-catalyzed α-alkylation of 1-pyridin-2-ylpiperidine (**3a**) using 2-methyl-2-vinyl-1,3-dioxolane (**2**).[a]



3a **2** (X equiv.) **4a** **5a**

Py = pyridin-2-yl

A = *trans*-cyclohexane-1,2-dicarboxylic acid
B = 3,4,5-trifluorobenzoic acic

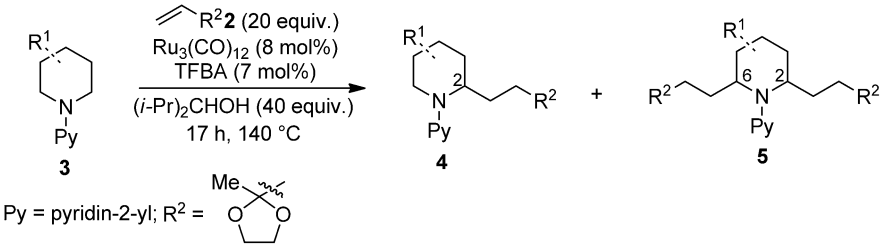
Entry	Acid[b]/[Ru] [mol%]	Initial loadings		Time [h]	GC yields [%][c]					Total Yield [%][f]
		2 [X equiv.]	ROH [Y equiv.]		**3a**	**4a**	**5a**[d]	remaining **2**[e]	reduced **2**[e]	
1	– (0/4)	10	5	24	85	12	2	43	55	14
2	A (4/4)	10	5	24	79	19	2	68	29	21
3	B (4/4)	10	5	24	72	23	5	70	28	28
4[g]	B (4/4)	10	5	24	71	23	6	65	30	29
5[g]	B (4/4)	10	15	24	58	31	12	22	76	43
6[g]	B (4/4)	10	40	24	46	35	19	0	95	54
7[g]	B (4/4)	20	5	24	63	28	8	73	25	36
8[g]	B (4/4)	20	15	24	54	29	17	66	31	46
9	B (4/4)	20	40	24	31	39	31	25	73	70
10	B (6/6)	20	40	24	25	38	38	14	83	76
11[h]	B (8/8)	20	40	24	17 (11)	38 (30)	44 (26)	10	88	82
12	B (9/8)	20	40	24	20	35	43	11	86	78
13[i]	B (7/8)	20	40	24	8	30	43	0	93	73
14	B (6/8)	20	40	24	20	38	40	5	92	78
15[h,j]	B (7/8)	20	40	17	10 (4)	44 (39)	46 (35)	2	90	90
16[h]	A (7/8)	20	40	17	25 (15)	40 (35)	33 (25)	5	90	73
17[h,j]	– (0/8)	20	40	17	60 (52)	31 (24)	7 (3)	0	97	38
18	– (0/8)	20	40	8	73	21	4	22	76	25

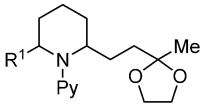
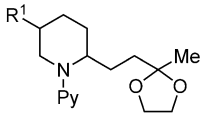
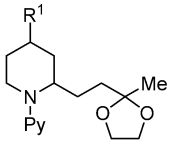
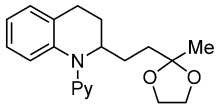
[a] All reactions were performed on a 0.5-mmol scale of **3a**.
[b] A = *trans*-cyclohexane-1,2-dicarboxylic acid, B = 3,4,5-trifluorobenzoic acid, [Ru] = $Ru_3(CO)_{12}$.
[c] Crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard, isolated yields are given in parenthesis.
[d] Sum of *trans*- and *cis*-**5a** isomers.
[e] Values are given with respect to the initial loading of **2** (*X*).
[f] Sum of the GC yields of **4a** and **5a**.
[g] Dodecane was used as a co-solvent, in order to keep the reaction volume constant.
[h] Reactions were performed on a 0.74-mmol scale of **3a** to derive isolated yields.
[i] The mass balance (81 %) and GC chromatogram indicated decomposition.
[j] GC yields represent the average of four experiments.

the role of the acid, which controls the rate of the functionalization of the piperidine substrate **3a** *versus* the reduction of the alkene **2**, an effect which was also observed in our alkylation protocol with unfunctionalized alkenes (Scheme 1).

We subsequently evaluated the substrate scope with respect to the substitution pattern of the piperidine in the coupling with alkene **2**. Gratifyingly, the synthetic protocol could be successfully applied to a number of piperidines featuring substituents in the 2-, 3-, and 4-positions, yielding compounds **4b–j** in moderate to good yields (Table 2). In the C-2 position, both small (methyl, **4b**) as well as large (phenyl, **4c**) substituents are well tolerated. This can be rationalized on the basis of pseudoallylic strain which places the C-2 substituent in an axial position on the piperidine ring, thereby avoiding steric hindrance with the directing group.[11] In the case of C-4 substituted piperidines (**4g–i**) a mixture of C-2 monoalkylated and C-2,6 bisalkylated piperidines was obtained, with the former being the major product observed. Both carbon-based (ester **4h**, phenyl **4i**) as well as heteroatom-based (ketal, **4g**) functional groups were tolerated at C-4. The compatibility of the protocol with an ester in C-4 of the piperidine ring is particularly interesting, as its presence makes the protons at C-4 quite acidic, creating a site for competitive functionalization.[12] Remarkably, the protocol was found to be fully regioselective for C-3 substituted piperidines (**3d–f**). The piperidine derivatives possessing a C-3 trifluoromethyl (**3d**), phenyl (**3e**) or methoxymethyl (**3f**) substituent all underwent smooth monoalkylation at the sterically

Table 2. Reaction scope for the Ru-catalyzed direct α-alkylation of substituted piperidines **3**.[a]



Entry	Product	R^1	Yield [%] 4[b]	5
1		**4b** (Me)	84 (22/62)	–
2		**4c** (Ph)	82 (20/62)	–
3		**4d** (CF_3)	63 (40/23)	–
4		**4e** (Ph)	75 (55/20)	–
5		**4f** (CH_2OMe)	66 (39/27)	–
6		**4g** ($O(CH_2)_2O$)	38	33[c]
7		**4h** (COOMe)	39 (26/13)	17[d]
8		**4i** (Ph)	34 (23/11)	18[e]
9		**4j**	74	–

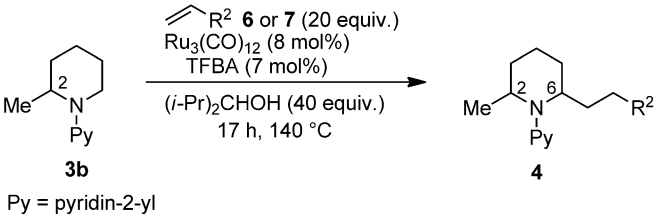
[a] Scale: **3b–f** (0.5–0.75 mmol, 1 equiv.).
[b] *dr* (*cis*:*trans*).
[c] For **5g**, *cis*:*trans* = 6:27.
[d] For **5h**, *dr* 4:5:8.
[e] For **5i** *dr* 9:4:5.

less hindered α-position, with the resulting 2,5-disubstituted piperidines (**4d–f**) being isolated in 63–75% yield. Regioselective monofunctionalization of C-3 substituted piperidines was also observed in our previously developed direct arylation protocol and therefore seems to be substrate controlled (sterics) and independent of the reagents used.[3i] For the 2,5-disubstituted piperidines (**4d–f**) resulting from this regioselective monoalkylation, the *cis*-diastereoisomer was observed to be the major reaction product, in contrast to what was observed for the 2,6-disubstituted piperidines (**4b**, **c**), where the *trans*-isomer was predominant. In addition, the effect of benzoannulation at the piperidine ring was also investigated, revealing that C-2 alkylated 1,2,3,4-tetrahydroquinoline (**4j**) could be obtained in very good yield (74%).

In continuation of our efforts to explore the reaction scope, we studied variations in the alkene component on piperidine **3b** under the conditions optimized for alkene **2**. We discovered that ketal-protected phenyl vinyl ketone (**6**) was equally well tolerated in the protocol, yielding **4k** in 87% yield (Table 3). In addition, ethyl 2,2-dimethyl-3-butenoate (**7**), featuring a 'locked' ester, also gave a high yield (87%) of the desired product **4l** (Table 3).

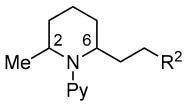
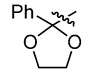
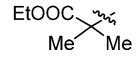
Bicyclic amines, which comprise a fused piperidine moiety, are structural entities of significant interest. In medicinal chemistry these scaffolds are used to obtain constrained analogues of interesting pharmaceutical compounds.[13] Some have even been launched as APIs, as exemplified by the smoke cessation agent Varenicline from Pfizer.[14] The locking of ring conformations and the steric hindrance associated with the bridge make bicyclic piperidines chemically challenging substrates for our direct functionalization process. Two examples were chosen to challenge our protocol: *N*-pyridin-2-yl-protected azabicyclo-[2.2.2]octane (isoquinuclidine) (**8**), which provides a 2,5-disubstitution pattern and locks the piperidine in a boat-like conformation, and *N*-pyridin-2-yl-protected 3-azabicyclo[3.2.1]octane (**10**) which features a 3,5-disubstitution pattern and locks the piperidine in a chair conformation (Scheme 3). Starting from isoquinuclidine **8**, alkylated **9** was derived in 47% yield.

Table 3. Alkene reaction scope for the Ru-catalyzed direct α-alkylation of **3b**.[a]

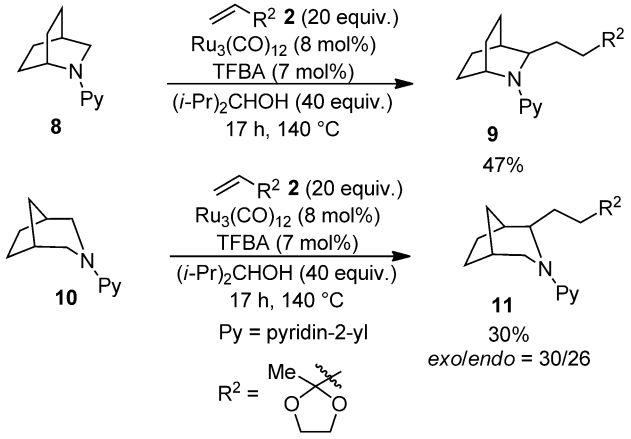


3b **4**

Py = pyridin-2-yl

Entry	Product	R^2	Yield [%] (*cis*/*trans*)
1		 **4k**	87 (22/65)
2		 **4l**	87 (22/65)

[a] Scale: **3b** (0.57 mmol, 1 equiv.).

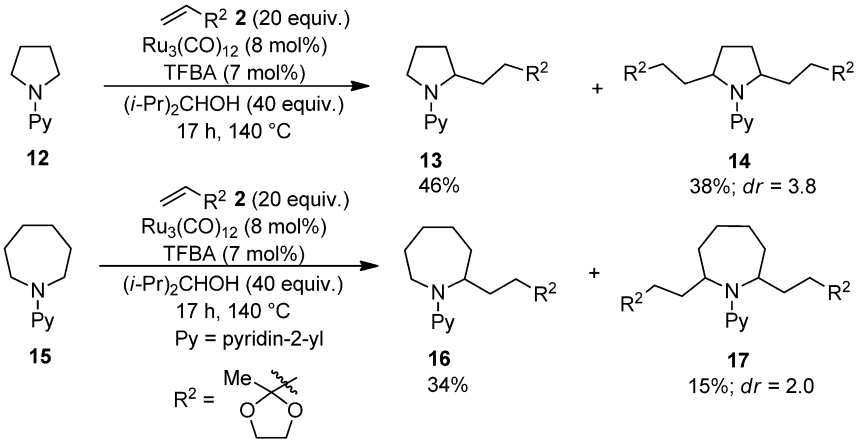


Scheme 3. Ru-catalyzed α-alkylation of bicyclic piperidines **8** and **10**.

This is remarkable, since the formation of 2,6-bis-alkylated products from C-3 substituted piperidines (**3d–f)** has never been observed before. Direct functionalization of bicyclic amine **10** proved also successful. Product **11** was obtained in 30% overall yield and the *exo*- and *endo*-diastereoisomers of **11** were separated by preparative HPLC.[15] To our delight, the use of both sterically congested bicyclic piperidines gave moderate yields under the developed reaction conditions without any further additional optimization. Not surprisingly, a significant amount of substrate was observed in the GC chromatogram of the reaction mixture of these challenging transformations. 2-Substituted 3-azabicyclo[3.2.1]octanes like **11** are especially interesting from an application point of view as they have, to the best of our knowledge, only been poorly explored.

As a final component to our study of the reaction scope, the suitability of the direct Ru-catalyzed alkylation protocol to functionalize smaller (pyrrolidine) and larger (azepane) saturated cyclic amines was also examined (Scheme 4). The application of the optimized reaction conditions on 1-pyridin-2-ylpyrrolidine (**12**) and 1-pyridin-2-ylazepane (**15**) gave the anticipated alkylated products in synthetically attractive yields. The high reactivity of **12** was manifested in a high overall yield of alkylated reaction products **13** and **14** (84%) and a low mono to bis reaction product ratio (1.2/1). This lends support to the proposed lower reactivity of piperidines *versus* pyrrolidines observed in other direct functionalization processes.[7] 1-Pyridin-2-ylazepane (**15**), gave a moderate overall yield (49%) and revealed the presence of a significant amount of starting material (28% GC yield) after 17 h, which suggests a lower reactivity of the azepane *versus* the piperidine ring system.

The assignment of the relative orientation (*cis* or *trans*) of the substituents in all the piperidine derivatives was done based on distinct differences in their



Scheme 4. Ru-catalyzed α-alkylation of 1-pyridin-2-ylpyrrolidine (**12**) and 1-pyridin-2-ylazepane (**15**).

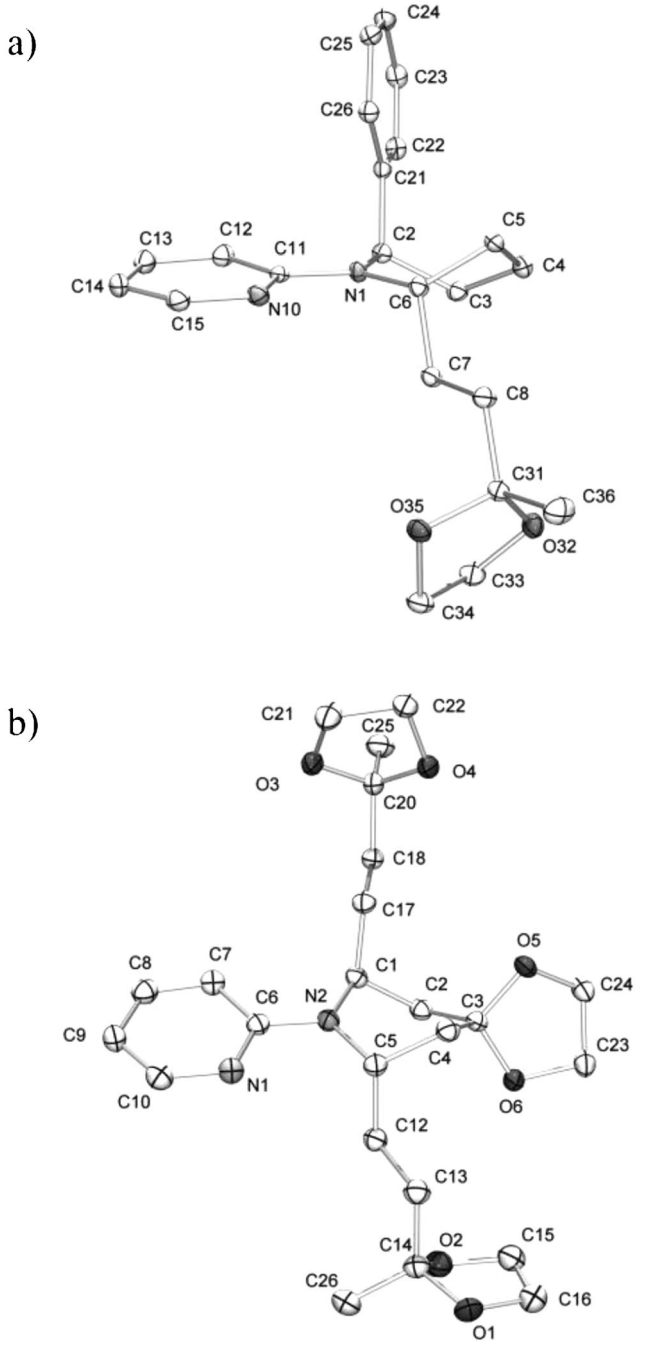


Figure 2. X-ray structure of a) *trans*-**4c**, b) *trans*-**5g** Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms, distorted solvent and (minor) disorder components are omitted for clarity.

^{1}H NMR spectra.[16] The multiplets representing the axial protons on the piperidine moiety were found shifted significantly upfield in comparison to the protons adopting equatorial positions. Structural assignment was additionally supported by the analysis of the observed coupling constants. In order to unequivocally confirm the relative orientation of the substituents, single crystal X-ray diffraction analysis was performed on representative compounds. Crystals were obtained for *trans*-**4c**, *trans*-**5g**, *cis*-**4e** and *cis*-**14** by slow evaporation of saturated solutions in heptane.[17] From X-ray structures of these compounds (Figure 2 and Figure 3), it appeared that the *N*-pyridinyl-2-yl moiety always adopts the thermodynamically favorable pseudoequatorial orientation. The central piperidine ring is significantly distorted to a twisted-boat conformation in *trans*-**4c** and *trans*-**5g** and features a pseudoaxial orientation of the substituents at the C-2 and C-6 positions in order to minimize steric hindrance with the pyridin-2-yl group at the neighboring nitrogen atom (Figure 2, a and b). In *cis*-**4e** (Figure 3, a) the central piperidine ring adopts a chair-like conformation with an equatorial orientation for the substituent at the C-5 position and an axial one for the substituent at C-2. For *cis*-**14** (Figure 3, b), the central pyrrolidine was noted to adopt an envelope-like conformation with pseudoaxial substituents at the corresponding C-2 and C-5 centers.

With the new synthetic protocol for direct alkylation in hand, we became interested in the potential for further synthetic transformations of the obtained α-functionalized products. The C-2 alkylated piperidine **4a** was selected as a model compound for this purpose. Application of our recently developed mild one-pot sequential protocol for pyridine DG removal[6] delivered piperidine **18** in an overall yield of 72% (Scheme 5). Hydrolysis of the dioxolane protective group in **4a** proceeded smoothly under catalytic acidic conditions delivering the 3-oxobutylpiperidine **19** in very high yield (93%), which we failed to synthesize directly from **3a** and methyl vinyl ketone (**1**) (Scheme 1).

Conclusions

An Ru-catalyzed protocol for the direct C(sp^3)–H α-alkylation of piperidines has been developed. This method permits one to efficiently introduce oxygen functionality (3-oxoalkyl) into the α-alkyl chain. Alkenones proved not to be useful reagents under the direct C(sp^3)–H functionalization conditions previously reported by our group. In order to avoid the inherent disadvantages of alkenes (i.e., reduction, polymerization, isomerization) a rational design of the alkene was required. By "masking" the keto functionality *via* dioxolane protection and further optimization of the reaction parameters an efficient protocol was achieved. Alternatively, locking of the conjugation of the double bond with a carbonyl as exemplified by ethyl 2,2-dimethyl-3-butenoate is also possible, thus circumventing the undesired isomerization to the more stable α,β-unsaturated carbonyl and further reduction anticipated with ethyl-3-butenoate as alkylating reagent. The versatility of the new protocol was

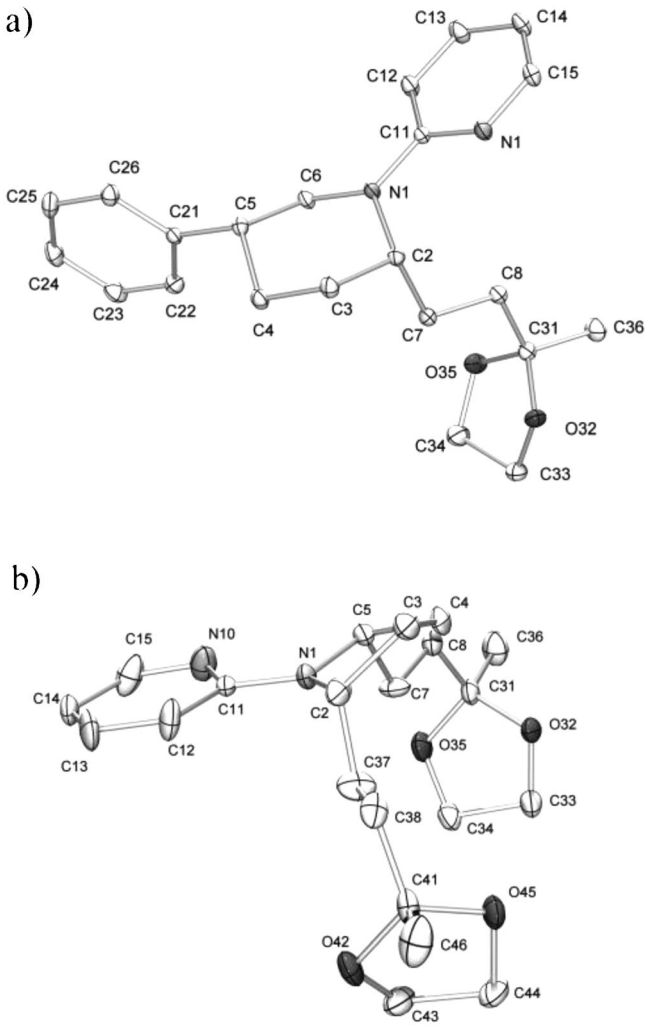
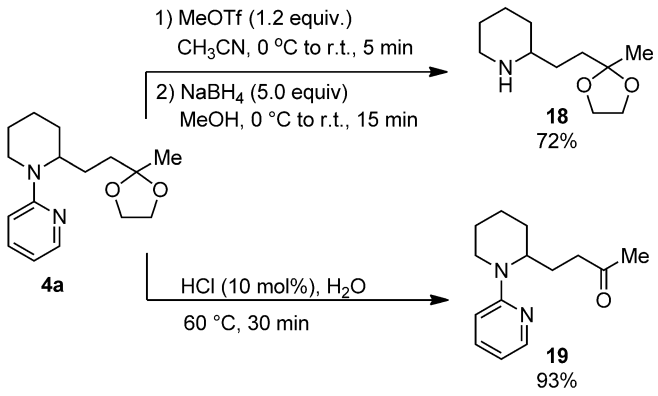


Figure 3. X-ray structure of a) *cis*-**4e**, b) *cis*-**14**. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms, distorted solvent and (minor) disorder components are omitted for clarity.



Scheme 5. Directing group removal and ketal deprotection in compound **4a**.

effectively demonstrated on a diverse set of piperidines, equipped with a pyridin-2-yl directing group. Piperidines with substituents in the C-2, C-4 positions were well-tolerated and delivered the anticipated monoalkylated and bisalkylated products in moderate to good yields. Regioselective α-alkylation of C-3 substituted piperidines was observed as a result of steric hindrance at the C-2 position. The assignment of the relative orientation of the substituents for the derived functionalized piperidines was done based on ^{1}H NMR spectroscopy and X-ray analysis. Challenging bicyclic amines, isoquinuclidine and 3-azabicyclo-[3.2.1]octane, featuring a bis-substituted piperidine entity were also effective substrates. In addition, the α-alkylation methodology was successfully demonstrated on other ring sizes (pyrrolidine and azepane systems). The utility of the α-alkylation methodology was demonstrated by the possibility to efficiently remove the pyridin-2-yl directing group as well as the ketal protective group in the reaction products. After all, post-transformation of the secondary amine and ketone functionalities will allow one to access a variety of substituted cyclic amines hitherto unknown and highly warranted for drug discovery purposes.

Experimental Section

General Procedure for Directed Ru-Catalyzed C(sp^3)–H α-Alkylation of Cyclic Amines Using Dioxolane Protected Alkenones

The reactions were performed on a 0.5–0.75-mmol scale of cyclic amine in 10 mL microwave vials. Each vial was equipped with a magnetic stirring bar and was charged with the appropriate *N*-pyridin-2-yl-substituted cyclic amine (1 equiv.), alkene (20 equiv.), a solution of 3,4,5-trifluorobenzoic acid (7.0 mol%) in 2,4-dimethyl-3-pentanol (40 equiv.) and $Ru_3(CO)_{12}$ (8.0 mol%). The vials were purged with argon and sealed by means of crimp caps. The vials were placed in an oil bath preheated at 140 °C. The cap was secured with a top clamp. The reaction mixtures were stirred for 17 h. After this time, the reaction vessels were cooled to ambient temperature, opened and the contents of all vials were combined. A commercially available ruthenium scavenger [Siliabond DMT, Silicycle, 0.2 g per 10 mg of $Ru_3(CO)_{12}$] was added along with dichloromethane (100 mL) and the resulting suspension was stirred at room temperature for 16 h. Subsequently, the solids were removed by filtration through a pad of Celite, which was additionally rinsed with dichloromethane (2×50 mL). The combined filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography using an automated flash chromatography system.

Alkylation of 3a with Alkene 2

The reaction was performed in four separate vials according to the general procedure described above. Each vial was charged with **3a** (120 mg, 0.74 mmol), a solution of 3,4,5-tri-

fluorobenzoic acid (9.1 mg, 0.05 mmol, 7 mol%) in 2,4-dimethylpentan-3-ol (3440 mg, 29.6 mmol), **2** (1690 mg, 14.8 mmol) and $Ru_3(CO)_{12}$ (37.8 mg, 0.06 mmol, 8 mol%). The crude products were purified by automated flash chromatography applying a heptane-ethyl acetate gradient (from 100% heptane to 50% heptane–50% ethyl acetate in 120 min, 40 mL min^{-1}).

2-{2-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]piperidin-1-yl}-pyridine (4a): yield: 320 mg (1.16 mmol, 39%); colorless viscous oil. ^{1}H NMR ($CDCl_3$): δ = 8.10 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.38 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 6.56 (d, *J* = 8.7 Hz, 1H), 6.45 (dd, *J* = 5.0, 7.0 Hz, 1H), 4.44–4.42 (m, 1H), 4.22–4.11 (m, 1H), 3.93–3.85 (m, 4H), 2.95 (td, *J* = 13.2, 2.8 Hz, 1H), 1.86–1.46 (m, 10H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 159.0, 147.7, 137.4, 111.5, 110.0, 106.7, 64.6, (2C) 51.4, 39.3, 36.0, 27.8, 25.3, 23.8, 23.0, 19.2; HR-MS (ESI): *m/z* = 277.1909, calculated for $C_{16}H_{25}N_2O_2^+$ $[M+H]^+$: 277.1916.

***trans*-2-{2,6-Bis[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]piperidin-1-yl}pyridine (*trans*-5a):** yield: 340 mg (0.87 mmol, 29%); colorless viscous oil. ^{1}H NMR ($CDCl_3$): δ = 8.15 (dd, *J* = 1.3, 5.0 Hz, 1H), 7.40 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 6.52 (dd, *J* = 6.5, 5.0 Hz, 1H), 6.47 (d, *J* = 8.6 Hz, 1H), 3.97–3.80 (m, 10H), 1.90–1.54 (m, 14H), 1.29 (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 158.7, 147.6, 136.6, 111.9, 110.0, 108.9, 64.5 (4C), 52.7, 36.2, 26.8, 24.5, 23.7, 15.0; HR-MS (ESI): *m/z* = 391.2602, calculated for $C_{22}H_{35}N_2O_4^+$ $[M+H]^+$: 391.2597.

***cis*-2-{2,6-Bis[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]piperidin-1-yl}pyridine (*cis*-5a):** yield: 65 mg (0.17 mmol, 6%); white solid; mp 125–127 °C. ^{1}H NMR ($CDCl_3$): δ = 8.10 (d, *J* = 3.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 6.44 (d, *J* = 7.8 Hz, 2H), 4.31 (m, 2H), 3.90–3.87 (m, 8H), 1.79–1.46 (m, 14H), 1.28 (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 158.4, 147.8, 137.2, 111.2, 110.0, 106.2, 64.5 (4C), 50.0, 37.0, 27.5, 23.8, 14.8; HR-MS (ESI): *m/z* = 391.2602, calculated for $C_{22}H_{35}N_2O_4^+$ $[M+H]^+$: 391.2597.

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