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The Role of the Alcohol and Carboxylic Acid in Directed Ruthenium-Catalyzed C(sp^3)–H α-Alkylation of Cyclic Amines

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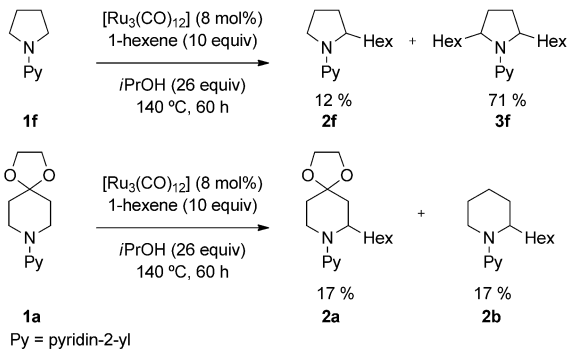
Abstract: A general directed Ru-catalyzed C(sp^3)–H α-alkylation protocol for piperidines (less-reactive substrates than the corresponding five-membered cyclic amines) has been developed. The use of a hindered alcohol (2,4-dimethyl-3-pentanol) as the solvent and catalyst activator, and a catalytic amount of *trans*-1,2-cyclohexanedicarboxylic acid is necessary to achieve a high conversion to product. This protocol was used to effectively synthesize a number of 2-hexyl- and 2,6-dihexyl piperidines, as well as the alkaloid (±)-solenopsin A. Kinetic studies have revealed that the carboxylic acid additive has a significant effect on catalyst initiation, catalyst longevity, and reverses the reaction selectivity compared with the acid-free reaction (promotes alkylation versus competing alkene reduction).

Keywords: acid effects · C–H activation · piperidines · ruthenium · selectivity

Introduction

C2-substituted piperidines are highly prevalent structural motifs in natural products and pharmaceuticals.[1] Therefore, the development of novel synthetic techniques for the direct C2–H functionalization of piperidines is of paramount importance. Several direct synthetic approaches have been described, for example via a C2 radical, anion, or cation intermediate, but these require a stoichiometric reagent.[2] Among these methods, direct C2 lithiation followed by reaction with electrophiles, pioneered by Beak,[3] has recently received significant renewed interest.[4] To date, examples of direct C2–H functionalization of piperidines by transition-metal catalysis are still rare.[5a–d,f] The direct functionalization studies published thus far have focused on pyrrolidines and only show (if any) a limited number of piperidine examples.[5] This is not surprising when the inherently lower reactivity of the six-membered ring system is considered relative to its five-membered counterpart. These important initial results in the field generally do not allow efficient piperidine functionalization as exemplified by our study on the direct C2 arylation of piperidines,[5d] in which the reaction conditions developed by Sames for pyrrolidines did not give synthetically useful results on piperidines.[5c] Recently, we performed direct C2 alkylation of piperidines and experienced a similar problem. Under the reaction conditions developed by Murai for pyrrolidine alkylation, piperidine substrate **1a** gave a poor conversion in a reaction with 1-hexene (Scheme 1).[5b] The reaction yielded only 17% of the 2-hexylated product **2a**, in addition to 17% of ketal-cleaved **2b** and 48% of recovered **1a** (Scheme 1). Surprisingly, GC-MS analysis of the crude reaction mixture at the end of the reaction revealed that 52% of the initial amount of hexene was converted to hexane and only 3.4% to alkylated products (**2a** and **2b**). Acetone was also observed in the reaction mixture, which clearly indicated that the isopropanol solvent acts as a hydrogen-transfer agent in this process.[6] There-



Scheme 1. C2 hexylation of **1f** and **1a** under Murai's reaction conditions.[5b]

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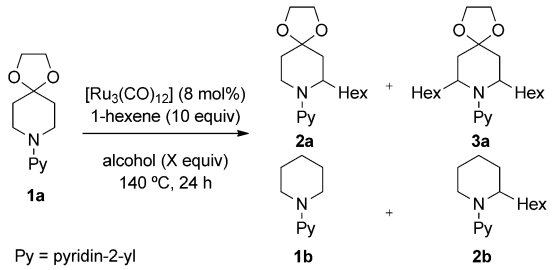
fore, identification of efficient alkylation conditions requires tuning of the two competitive reactions (alkylation versus reduction). Herein, we report that a catalytic amount of a carboxylic acid additive can be used to achieve this goal.

Results and Discussion

As the alcohol acts as a reagent in competitive reduction reactions, we tested *t*BuOH as a solvent that cannot act as a hydrogen transfer agent. However, very little substrate consumption was observed (Table 1, entry 4), which points towards an active role of the alcohol in the alkylation reaction mechanism. Primary alcohol *n*BuOH gave a slightly better conversion to the desired reaction products than *i*PrOH (Table 1, entry 1 versus 2). Interestingly, the use of 2,4-dimethyl-3-pentanol (a more sterically hindered secondary alcohol that is harder to oxidize) gave more of the desired alkylated products and completely suppressed the ketal reduction (Table 1, entry 3).[7] Therefore, this alcohol was selected as the solvent for further studies. The reaction with 2,4-dimethyl-3-pentanol (10 equiv), in which the "inert" solvent *t*BuOH was used to make up the difference in volume relative to the standard experiment, showed a decrease in substrate conversion (Table 1, entry 5 versus 3). This result further supports the active role of the alcohol in the alkylation reaction. Reduction of the amount of alcohol (26 to 10 to 5 equiv) led to an increase in the conversion of **1a** into **2a** and **3a** (Table 1, entries 6 and 7), presumably due to a concentration effect. Further decrease of the alcohol content appears to be detrimental as less substrate consumption was observed (Table 1, entry 8), thus, 5 equivalents of 2,4-dimethyl-3-pentanol were taken as the optimal alcohol stoichiometry.

Table 1. The effect of the alcohol structure and loading on the hexylation of **1a**.

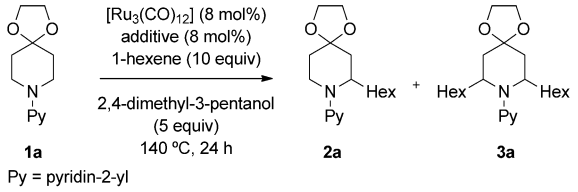


Entry	Alcohol	X	**1a**[a]	**2a**[a]	**3a**[a,b]	**1b**[a]	**2b**[a]
1	*n*BuOH	26	53	40	0	2	5
2	*i*PrOH	26	61	23	0	7	9
3	2,4-dimethyl-3-pentanol	26	57	39	4	0	0
4	*t*BuOH	26	90	10	0	0	0
5	2,4-dimethyl-3-pentanol[c]	10	71	27	2	0	0
6	2,4-dimethyl-3-pentanol	10	45	49	6	0	0
7	2,4-dimethyl-3-pentanol	5	38	54	8	0	0
8	2,4-dimethyl-3-pentanol	2.5	50	45	5	0	0

[a] Corrected GC-FID conversions. [b] Compound **3a** is a mixture of diastereoisomers. [c] Reaction volume increased to 1.82 mL by addition of *t*BuOH (volume when *i*PrOH (26 equiv) is used, see entry 2).

To further optimize the alkylation reaction, the effect of additives was investigated (Table 2). Interestingly, carboxylic acids tended to further increase the conversion to alkylated products. Carboxylates are known to facilitate a number of different transition-metal catalyzed C(sp^2)–H functionalizations,[8] but only in rare cases do these reactions occur under acidic conditions.[9] The use of *trans*-1,2-Cy(COOH)$_2$ (Cy = cyclohexane; Table 2, entry 4) was found to be particularly effective and led to 93% conversion. The lower conversion and inhibition observed with *cis*-1,2-Cy(COOH)$_2$ and phthalic acid, respectively, indicates the importance of spatial arrangement when dicarboxylic acids are used (Table 2, entries 5 and 11). Benzoic acid additives generally give good conversion, but when the acidity becomes too high the conversion ultimately drops (Table 2, entries 6–10). The best result was obtained with 3,4,5-trifluorobenzoic acid, which led to a conversion of 89% (Table 2, entry 9).[10] In contrast, when the reaction was performed with other types of acid it was significantly inhibited in comparison to the additive-free reaction (Table 2, entries 12–14 versus 1). Surprisingly, the use of potassium carboxylates provided lower conversions than those obtained with the corresponding carboxylic acids (Table 2, entries 15 and 16 versus 2 and 9). These results clearly demonstrate the necessity for the additive to possess both a carboxylate structural entity and an acidic proton.

Table 2. The effect of additive on the hexylation of **1a**.



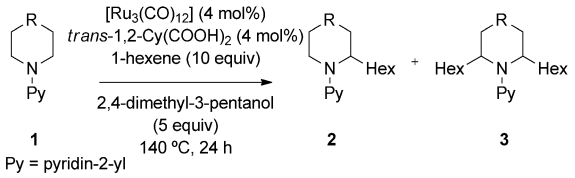
Entry	Additive	pK_a	**1a**[a]	**2a**[a]	**3a**[a,b]
1	–	–	38	54	8
2	AcOH	3.58	18	63	19
3	PivOH	5.01	26	60	14
4[c,d]	*trans*-1,2-Cy(COOH)$_2$	4.18, 5.93	7	65	28
5	*cis*-1,2-Cy(COOH)$_2$	4.34, 6.76	17	64	19
6	(4-MeO)C$_6$H$_4$COOH	4.53	25	60	15
7	PhCOOH	4.20	23	61	16
8	(4-F)C$_6$H$_4$COOH	4.14	17	62	21
9	(3,4,5-tri-F)C$_6$H$_2$COOH	3.46	11	59	30
10	C$_6$F$_5$COOH	1.60	25	60	15
11	phthalic acid	2.98, 5.28	90	10	0
12	*p*-TsOH	1.99	57	40	3
13	Py·HCl	5.21	46	47	7
14	Et$_3$N·HCl	10.75	48	46	6
15	AcOK	–	62	35	3
16	(3,4,5-tri-F)C$_6$H$_2$COOK	–	83	16	1

[a] Corrected GC-FID conversion. [b] Compound **3a** is a mixture of diastereoisomers. [c] An experiment without [Ru$_3$(CO)$_{12}$] catalyst under otherwise identical reaction conditions showed no conversion to product. [d] When [Ru$_3$(CO)$_{12}$] (4 mol%) and *trans*-1,2-Cy(COOH)$_2$ (4 mol%) were used a conversion of 2:59:39 (**1a**/**2a**/**3a**) was observed.

The $[Ru_3(CO)_{12}]$ loading could be reduced to 4 mol% without sacrificing conversion (Table 2, entry 4). The catalyst/carboxylic acid ratio was screened for the two best performing acid additives, *trans*-1,2-Cy(COOH)$_2$ and 3,4,5-trifluorobenzoic acid. In general, good conversion can be achieved by using a 1:1 ratio of catalyst to additive, but higher loadings of acid inhibited the reaction (see the Supporting Information).

With the optimized conditions in hand (**1a** (1 equiv), 2,4-dimethyl-3-pentanol (5 equiv), 1-hexene (10 equiv), $[Ru_3(CO)_{12}]$ (4 mol%), *trans*-1,2-Cy(COOH)$_2$ (4 mol%), 140 °C , 24 h), the substrate scope was assessed. Under these reaction conditions, both unsubstituted piperidine **1b** and C4-substituted piperidines **1a**, **1c**, and **1d** were hexylated efficiently to deliver good yields of mono- and dialkylated products **2** and **3** (Table 3, entries 1–4). Piperidine **1e** proved

Table 3. Hexylation of cyclic amines **1** under the optimized reaction conditions.

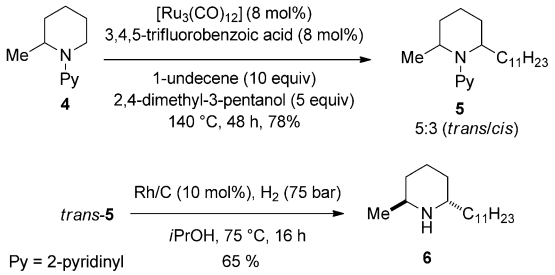


Entry	1	R	2	Yield [%][a]	3	Yield [%][a]
1	**1a**		**2a**	48	**3a**	43[b]
2	**1b**		**2b**	26	**3b**	43[c]
3	**1c**		**2c**	39[d]	**3c**	47[e]
4	**1d**		**2d**	32[f]	**3d**	53[g]
5	**1e**		**2e**	–	**3e**	76[h]
6	**1f**	(pyrrolidine)	**2f**	26	**3f**	70[i]

[a] Isolated yield. [b] *Trans*/*cis* ratio = 1:1, compound **1a** (2%) was also isolated. [c] *Trans*/*cis* ratio = 2:1. [d] *Trans*/*cis* ratio = 1:1. [e] Diastereomeric ratio (d.r.) = 9:3:1. [f] *Trans*/*cis* ratio = 1:3. [g] d.r. = 4:1:1, compound **1d** (12%) was also isolated. [h] d.r. 2:6:1, $[Ru_3(CO)_{12}]$ (8 mol%) and *trans*-1,2-Cy(COOH)$_2$ (8 mol%) were used; compound **1e** (9%) was also isolated. [i] *Trans*/*cis* ratio = 5:3.

to be less reactive, therefore a double catalyst and acid loading (8 mol%) was used, in this case only the dihexylated product **3e** was obtained (Table 3, entry 5). Gratifyingly, the standard reaction conditions also proved suitable for pyrrolidine **1f** (Table 3, entry 6). Compared with the original Murai conditions (Scheme 1), our reaction conditions require half of the original catalyst loading and a reaction time of 24 h rather than 60 h.

To further showcase the potential of the newly developed alkylation procedure, we devised a new route to (±)-solenopsin A (**6**) starting from 2-methyl-(1-pyridin-2-yl)piperidine (**4**).[11] A slow conversion to undecylated product (**5**) was observed, which is a result of the catalyst isomerizing the 1-undecene reagent to yield a mixture of nine undecenes in comparison with five in the 1-hexene case. Hence, the longer the chain, the more challenging the coupling, due to a lower concentration of the reactive terminal alkene. The use of the 1:1 $[Ru_3(CO)_{12}]$/3,4,5-trifluorobenzoic acid (8 mol%) catalyst system over 48 h was found to be optimal for C6 undecylation of **4** (see the Supporting Information).[12] Piperidine **5** was isolated in 78 % yield as a 5:3 (*trans*/*cis*) diasteriomeric ratio (Scheme 2). Hydrogenation of the pyridine ring of *trans*-**5** with Rh/C under H_2 pressure allowed efficient directing group removal in a single step to provide 65% of (±)-solenopsin A (Scheme 2).



Scheme 2. Synthesis of (±)-solenopsin A (**6**).

To rationalize the effect of the carboxylic acid on the rate of the catalysis, we analyzed the conversion of substrate **1a** into products **2a** and **3a** as a function of time, both in the absence and presence of *trans*-1,2-Cy(COOH)$_2$ (Figures 1a and b). Comparison of the kinetic profiles confirmed a faster reaction in the presence of the acid, and also revealed that without acid the reaction onset was much slower (>1 h induction period; Figure 1a). Additionally, in the absence of acid catalyst deactivation is observed after 6 h and conversion reaches a plateau after 10 h (Figure 1a). In contrast, the reaction in the presence of a catalytic amount of *trans*-1,2-Cy(COOH)$_2$ showed essentially no initiation period and sustained conversion to alkylated products was observed over the full 24 h reaction time (Figure 1b). This implies that the acid additive is involved in the catalyst activation process and, moreover, increases catalyst longevity. Interestingly, further analysis of the kinetic data revealed that the selectivity for alkylation versus reduction is reversed. Without the acid additive the rate of hexene reduction is far greater than that of the alkylation reaction (ca. ×5), whereas in the presence of acid the alkylation reaction becomes the major reaction pathway (Figure 1c). This is in accordance with a reduced rate of alcohol oxidation to ketone found in the presence of *trans*-1,2-Cy(COOH)$_2$ (Figure 1d).

To further understand the reaction dependence upon reagent stoichiometry, a number of kinetic analyses in the presence of acid additive were performed by alteration of the quantities of 1-hexene and 2,4-dimethyl-3-pentanol used. The overall reaction concentration was maintained by keep-

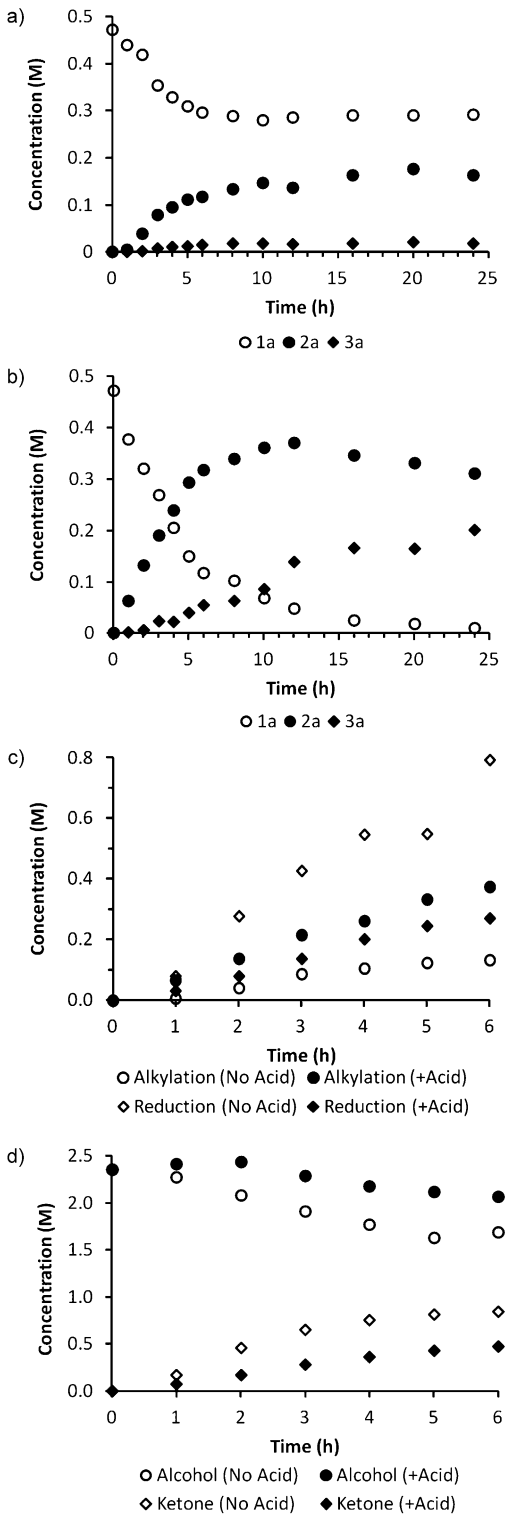
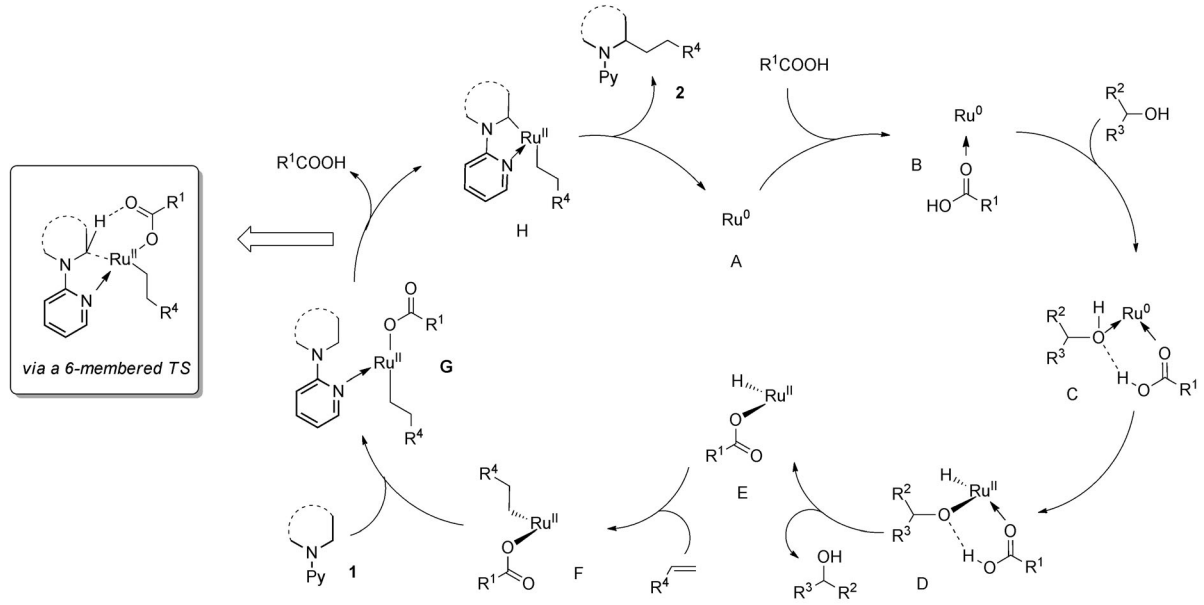


Figure 1. Kinetic profiles for the reaction of **1a** (0.5 mmol) with 1-hexene (5 mmol) in 2,4-dimethyl-3-pentanol (2.5 mmol) in the presence of $[Ru_3(CO)_{12}]$ (4 mol%): a) in the absence of acid additive, b) in the presence of *trans*-1,2-Cy$(COOH)_2$ (4 mol%). c) Selectivity of reduction (hexane formation ≡ [hexane]) versus alkylation (formation of **2a** and **3a** ≡ [**2a**]+2[**3a**]) in the absence or presence of *trans*-1,2-Cy$(COOH)_2$ (4 mol%). d) Oxidation of 2,4-dimethyl-3-pentanol to 2,4-dimethyl-3-pentanone in the absence or presence of *trans*-1,2-Cy$(COOH)_2$ (4 mol%).

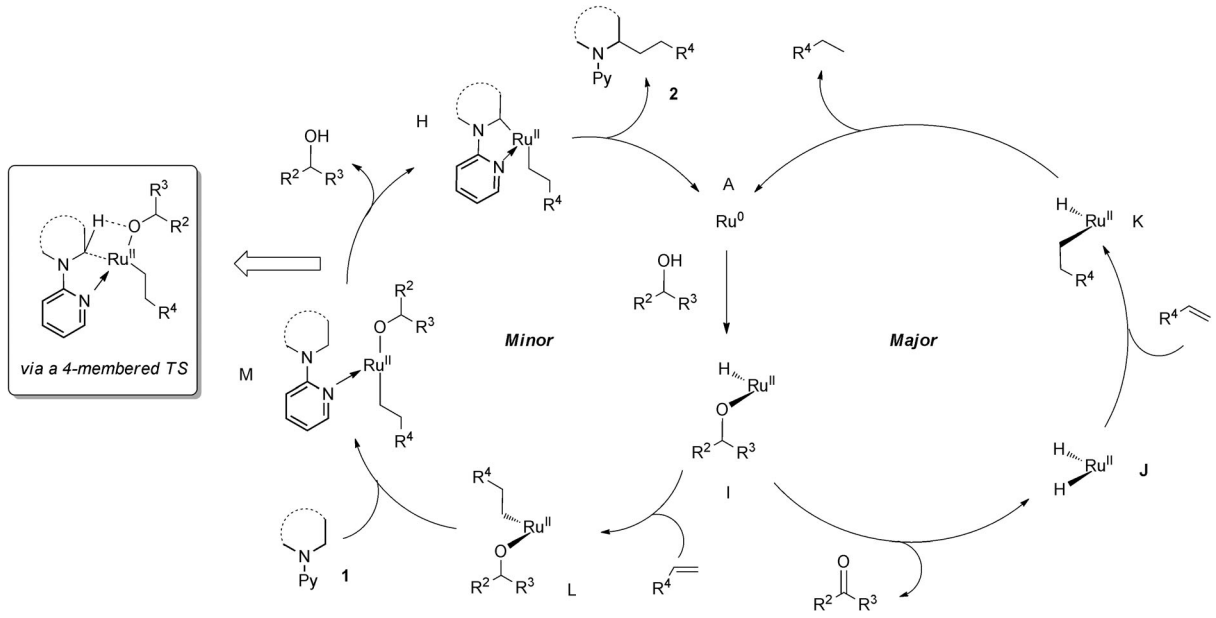
ing the total volume equal by the addition of dodecane. When the reaction was performed with varying amounts of olefin the rate of the reaction, under the optimized reaction conditions, increased with the number of equivalents of 1-hexene (5, 10, and 15 equiv; see the Supporting Information) used. The k_{obsd} was found to exhibit a pseudo-first-order dependence with respect to the hexene concentration (see the Supporting Information). The conversion of substrate as a function of time in the presence of *trans*-1,2-Cy$(COOH)_2$ with various concentrations of alcohol (see the Supporting Information) revealed no significant overall rate effect. In the presence of more alcohol (10 equiv relative to 5 or 2.5 equiv), the reaction showed a short induction period, similar to what was observed when no acid was added. However, the conversion was almost complete after 24 h, which indicates that the catalyst remains active throughout the course of the reaction when acid is present. It is important to note that in the absence of Ru acid alone does not allow catalysis to occur; no conversion was obtained (Table 2, entry 4). Reactions performed 1) without 2,4-dimethyl-3-pentanol and 2) with *t*BuOH to replace 2,4-dimethyl-3-pentanol, both in the presence of *trans*-1,2-Cy$(COOH)_2$, gave little alkylation product (see the Supporting Information). Conversions of **1a** to **2a** were only 10 and 14%, respectively, and **3a** was not present. These experiments indicate that when there is no acid present, the alcohol is solely responsible for the catalyst activation. However, in the presence of acid, both the acid and the alcohol are involved in the catalyst activation process. These results can be rationalized based on competitive binding of the acid and alcohol to Ru^0. This is also in accordance with the results obtained when a higher *trans*-1,2-Cy$(COOH)_2$/$[Ru_3(CO)_{12}]$ ratio was used; catalysis was inhibited when the same amount of alcohol was present (see the Supporting Information).

Based on the experimental data, a mechanistic proposal for directed Ru-catalyzed C(sp^3)–H alkylation is given in Scheme 3.[13] Hydrogen bonding between the hydroxyl groups of the carboxylic acid and the alcohol bound to Ru^0 (**C**)[14] facilitates oxidative addition of the alcohol. The bound carboxylic acid can release the alcohol by protonation to yield $H–Ru^{II}–OOCR^1$ (**E**), which is the catalytically active species. Subsequent alkene insertion, which is the rate-limiting step based on the observed rate dependence on the concentration of the alkene, provides **F**. Upon coordination of substrate **1**, the ruthenium-bound carboxylate assists in the C–H activation step by a concerted metalation–deprotonation (CMD) type mechanism to reform the carboxylic acid.[15] Reductive elimination finally yields alkylated compound **2** (and after a second cycle, compound **3**) and regenerates Ru^0.

The reversal of preference for alkylation versus reduction in the presence of acid can be rationalized by analysis of the mechanism of hexane formation in the absence of acid (Scheme 4). Ruthenium alkoxide (**I**), formed by oxidative addition of an alcohol, can produce a ruthenium dihydride species (**J**), which yields the undesired alkane upon alkene



Scheme 3. Plausible mechanism for alkylation in the presence of a carboxylic acid additive.



Scheme 4. Plausible mechanisms for alkylation (minor) and alkene reduction (major) in the absence of a carboxylic acid additive.

insertion and subsequent reductive elimination (via **K**). This process can be slowed through protonation of the alkoxide by bound carboxylic acid, which is in accordance with the reduced amount of alkene reduction (less alkane and ketone formation) and increased rate of alkylation observed in the presence of a carboxylic acid additive. When no carboxylic acid is added, β-hydride elimination, which leads to alkene reduction, is not inhibited and is, therefore, more pronounced versus the C(sp^3)–H functionalization process. In the absence of acid, the C–H activation step occurs in complex **M** through a four-membered transition state that involves bound alkoxide in place of carboxylate.

Conclusion

We have discovered that carboxylic acid additives improve the directed ruthenium-catalyzed C(sp^3)–H alkylation of cyclic amines with alkenes. For less-reactive ring sizes (piperidine) the acid additive is crucial to achieve full conver-

sion of substrate. Carboxylic acid improves catalyst activation, catalyst longevity, and induces a profound selectivity shift (undesired alkene reduction versus desired alkylation). The role of the acid presented here is unprecedented in direct transition-metal-catalyzed C(sp^3)–H functionalizations and will stimulate new advances in this challenging field. As an application of the methodology, the alkaloid (±)-solenopsin A was synthesized.

Experimental Section

General procedure for 2-hexylation of 1-(pyridin-2-yl)piperidines: Two microwave pressure vials (10 mL) were each charged with the appropriate 1-(pyridin-2-yl)piperidine or 1-(pyridin-2-yl)pyrrolidine (0.5 mmol), [$Ru_3(CO)_{12}$] (12.8 mg, 0.02 mmol, 4.0 mol%), *rac-trans*-cyclohexane-1,2-dicarboxylic acid (3.4 mg, 0.02 mmol, 4 mol%), 2,4-dimethyl-3-pentanol (350 μL, 2.5 mmol, 5 equiv), and 1-hexene (625 μL, 5.0 mmol, 10 equiv). The vials were purged with Ar and sealed with crimp caps. Subsequently, the reaction vials were placed in a preheated oil bath at 140 °C for 24 h (the cap was secured with a vial top clamp). After the allotted reaction time, the content from both vials were combined in a round-bottomed flask and reduced in vacuo. The products were isolated by flash chromatography on silica gel.

Acknowledgements

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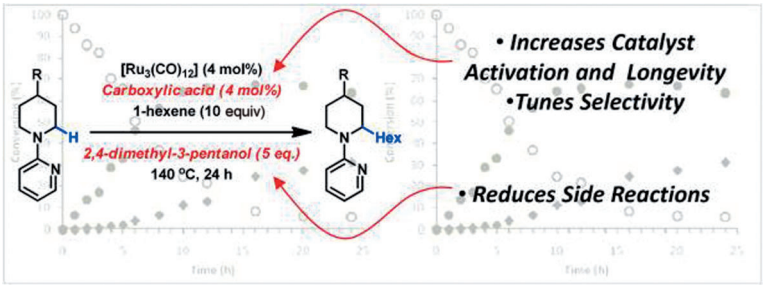

Acid makes the difference! A directed Ru-catalyzed C(sp^3)–H α-alkylation protocol for cyclic amines has been developed (see scheme). Kinetic studies revealed that the carboxylic acid aids catalyst activation, increases catalyst longevity, and reverses the reaction selectivity. The alcohol selected as the solvent plays an active role in the catalysis.

C–H Activation

*S. D. Bergman, T. E. Storr, H. Prokopcová, K. Aelvoet, G. Diels, L. Meerpoel, B. U. W. Maes** ..... ▮▮▮▮–▮▮▮▮

The Role of the Alcohol and Carboxylic Acid in Directed Ruthenium-Catalyzed C(sp^3)–H α-Alkylation of Cyclic Amines