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Rhodium-Catalyzed C−H Methylation and Alkylation Reactions by Carbene-Transfer Reactions

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Abstract: In this combined computational and experimental study, the C−H functionalization of 2-phenyl pyridine with diazoalkanes was investigated. Initial evaluation by computational methods allowed the evaluation of different metal catalysts and diazoalkanes and their compatibility in this C−H functionalization reaction. With these findings, suitable reaction conditions for the C−H methylation reactions were quickly identified by using highly reactive TMS diazomethane and C−H alkylation reactions with donor/acceptor diazoalkanes, which is applied to a broad scope on alkylation reactions of 2-aryl pyridines with TMS diazomethane and donor/acceptor diazoalkane (51 examples, up to 98% yield).
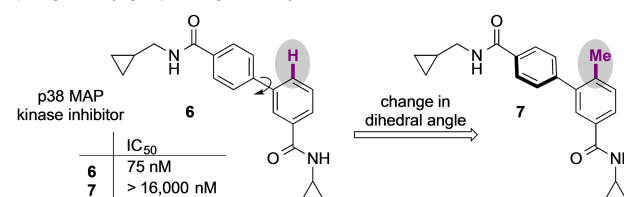
Introduction

The C−H functionalization with carbene or metal carbene intermediates constitutes an important strategy to increase molecular complexity for the introduction of novel functional groups. The high reactivity of the carben(oid) intermediate renders this approach particularly useful and it allows, for example the direct C−H functionalization of aliphatic hydrocarbons in a catalyst-controlled approach without the need of (transient) directing groups.[1,2] On the contrary, the use of directing groups in C−H functionalization reaction employing carbene or metal carbene intermediates is much less explored.[3] The vast majority of approaches focus on the application of acceptor/acceptor diazoalkanes, derived from dialkyl malonates (Scheme 1a).[4] In this context, the use of TMS-diazomethane is surprisingly underdeveloped, although such reaction would allow the introduction of a methyl group.[5] The introduction of the latter onto molecular scaffolds is often considered as a minor structural modification. However, the effect of a methyl group on the pharmacological profile of drugs can be very significant and can result in fundamentally shifted physical-chemical properties, metabolic stability, or binding to the biological target.[6] One of first examples, was reported in 2008 by GSK chemists, which describes the improvement of target binding by 100–1000-fold upon introduction of a single methyl group (Scheme 1b).[6b] Despite the small structural changes, the key challenge for the synthesis of "methylated" analogues of
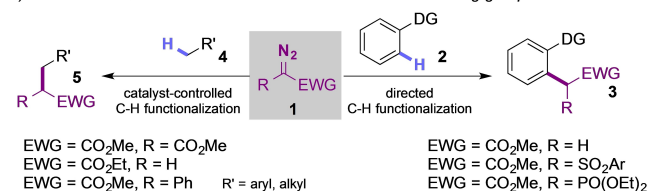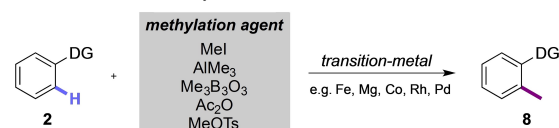

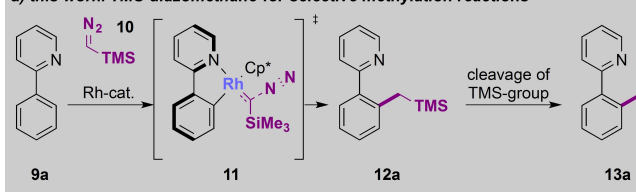**Scheme 1.** a) Diazoalkanes in directed and catalyst-driven C−H functionalization. b) Magic methyl groups in drug discovery. c) Transition-metal directed methylation reactions. d) TMS-Diazomethane for selective methylation reactions. DG=directing group.

drug molecules lies within the exploration of de novo synthesis routes due to the scarcity of available synthesis methods for direct C−H methylation reactions. As a result, the development of such synthesis methods to directly introduce a methyl group onto an existing scaffold is in high demand to increase step-

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economy and to allow the introduction of a methyl group on drugs or drug-like molecules. To achieve this goal, a number of different approaches have been realized employing transition metal-catalyzed C—H activation or photoredox catalysis for the installation of the pivotal C_1-building block. Typical reagents used as C1-building block in transition metal-catalyzed C—H activation are methyl iodide, methylated boron-based reagents, sulfonium salts, acetic acid, and more lately peroxides (Scheme 1c).[7,8] The latter constitute today an important class of reagents to liberate a methyl radical that in turn can be used under metal-catalyzed conditions in C—C bond forming reactions.[7c,d]

One of the most simple C_1-synthons for such a direct C—H functionalization represents methylene, which is the most simple carbene. Despite a long tradition of carbene transfer reactions in C—H functionalization chemistry, the introduction of a methyl group via carbene transfer reactions is surprisingly underdeveloped.[9] One of the few examples represents an early report by Meerwein, who reported on the photolysis reaction of diazomethane and unspecific C—H methylation reaction of diethyl ether solvent.[9] However, the high reactivity of diazomethane poses significant hazards and thus synthetic feasibility is significantly hampered. An alternative reagent represents TMS diazomethane, which could be amenable for the introduction of a methyl group following desilylation (Scheme 1d).

Results and Discussion

Theoretical studies on the reaction mechanism

We commenced our studies on C—H functionalization reactions with TMS diazomethane (**10**) by using 2-phenyl pyridine (**9a**) as a model substrate, which can be regarded as one of the key substrates to demonstrate an initial proof of concept. To achieve this goal, we first aimed at understanding this C—H functionalization reaction on a theoretical basis and thus examined three archetypal metal salts to identify the most suitable catalyst at 80 °C reaction temperature. These reactions proceed via an initial cyclometalation of 2-phenyl pyridine followed by a ligand exchange with TMS diazomethane and nitrogen extrusion to give the corresponding cyclometalated complex with a carbene ligand. Subsequent migratory insertion and consecutive ligand exchange gives the C—H functionalization product. This general mechanism is in accordance with previous proposals and now provides first computational evidence of the key reaction steps. The energy profile of this process is strongly dependent on the metal salt under investigation. In the case of a Rh(III) salt, all reaction steps proceed via low-lying transition states that indicate the general feasibility of a Rh-catalyzed C—H alkylation reaction with TMS diazomethane. On the contrary, the C—H alkylation reaction for iridium or ruthenium salts is disfavored. For iridium, the calculations show a facile ligand exchange and carbene formation, however the migratory insertion is strongly disfavored and requires a high activation free energy (29.7 kcal/mol) that renders this process unfavorable. In the case of ruthenium
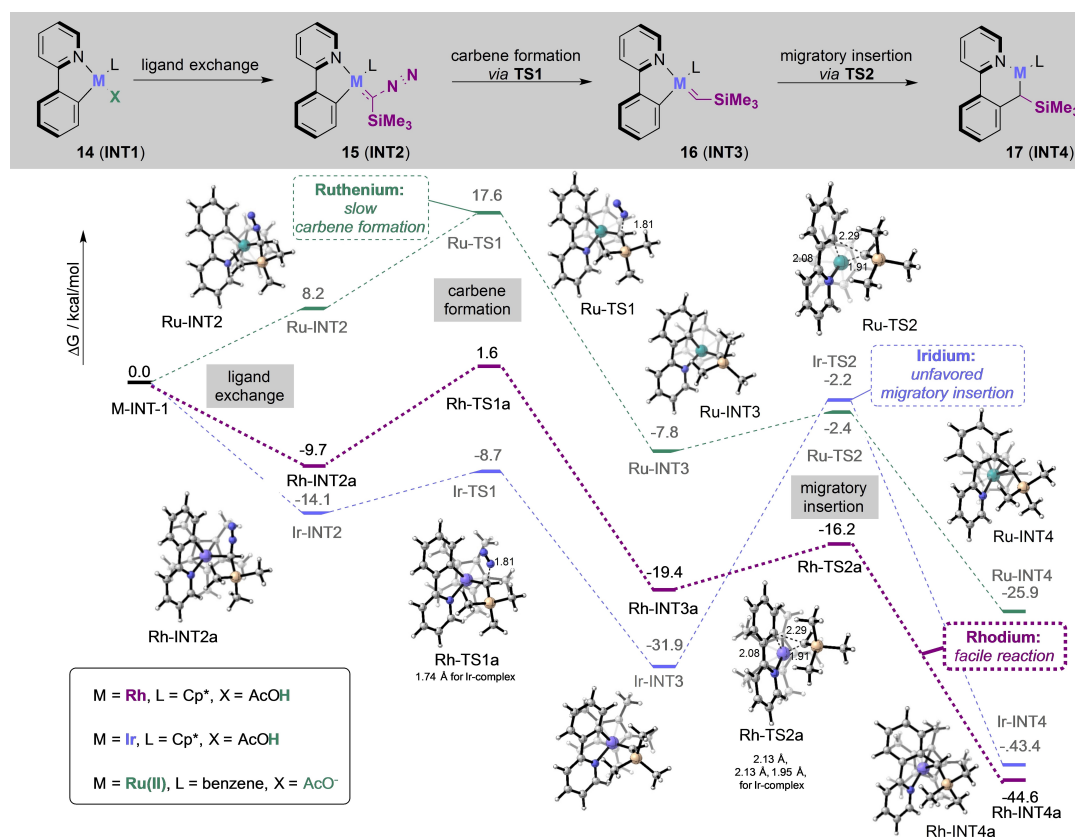
salts, the initial ligand exchange and subsequent metal carbene formation is energetically disfavored and requires a substantially higher activation free energy (17.6 kcal/mol). This high energy barrier slows down the process, which can rapidly lead to thermal decomposition of TMS diazomethane (Scheme 2).

In a next step, we analyzed the influence of the electronic properties of the diazoalkane reaction partner on this C—H functionalization reaction. In comparison to the above analysis of different metal catalysts, differences in the reaction of electronically distinct diazoalkanes are much smaller. Importantly the initial ligand exchange is readily feasible for all diazoalkanes under investigation. For TMS diazomethane the process is energetically most favored (−9.7 kcal/mol), while other complexes with diazoalkanes show only minor changes in energy compared to complex **Rh-INT1** (−2.8 to 3.1 kcal/mol). Subsequent release of nitrogen gas via low lying **Rh-TS1** results in a facile formation of metal carbene complex **Rh-INT2** for all diazoalkanes under investigation (Scheme 3).

The calculations further revealed that migratory insertion takes place with similar energy barriers for all diazoalkanes used in this theoretical study (1.9–5.2 kcal/mol, for details please see the Supporting Information). In a last step, the C—H functionalization product is released. Therefore, such C—H functionalization reaction of 2-phenyl pyridine should be feasible at 80 °C with a broad variety of diazoalkane reaction partners and it surprising that only acceptor-type diazoalkanes were studied until now.

Application in synthesis

Based on the above calculations, we were convinced that C—H functionalization reaction of 2-phenyl pyridine (**9a**) with TMS diazomethane (**10**) and donor/acceptor diazoalkanes should be feasible and therefore commenced with the experimental studies on this reaction. As expected, a good yield of the desired C—H functionalization product **12a** was obtained in the presence of [Cp*RhCl₂]₂ as catalyst (Table 1, entry 1). A substantially lower yield was observed in the case of [Ru(cymene)Cl₂]₂ and only traces of the reaction product **12a** were obtained with [Cp*IrCl₂]₂ as catalyst while the decomposition of TMS diazomethane was observed in both cases (Table 1, entries 2,3). When using Cp*Co(CO)I₂ as catalyst no product formation was observed and **10** decomposed (Table 1, entry 4). In the absence of AgSbF₆, no reaction occurred. Further studies on the role of the solvent, acetate salt, reaction temperature and the addition time of the TMS diazomethane (**10**) did not improve the reaction yield (Table 1, entries 5–7). Of all solvents investigated, 1,2-DCE proved to be optimal and a significantly reduced yield was obtained in almost all other solvents. Notably, when using DMSO or methanol as solvent, a moderate yield of the C—H functionalization product was obtained (for details, please see Table S1 in Supporting Information). NaOAc was identified to be by far superior over other bases and only moderate yields of **12a** were obtained when using other acetate salts (for details, please see Table S1 in Supporting Information).

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Scheme 2. Theoretical studies on Rh, Ir, and Ru metal-salts in C–H functionalization of 2-phenyl pyridine with TMS diazomethane. Calculations were performed at BP86-D3/6-311 + +G(d,p)/def2tzvpp// BP86-D3/6-31G(d,p)/SDD level.
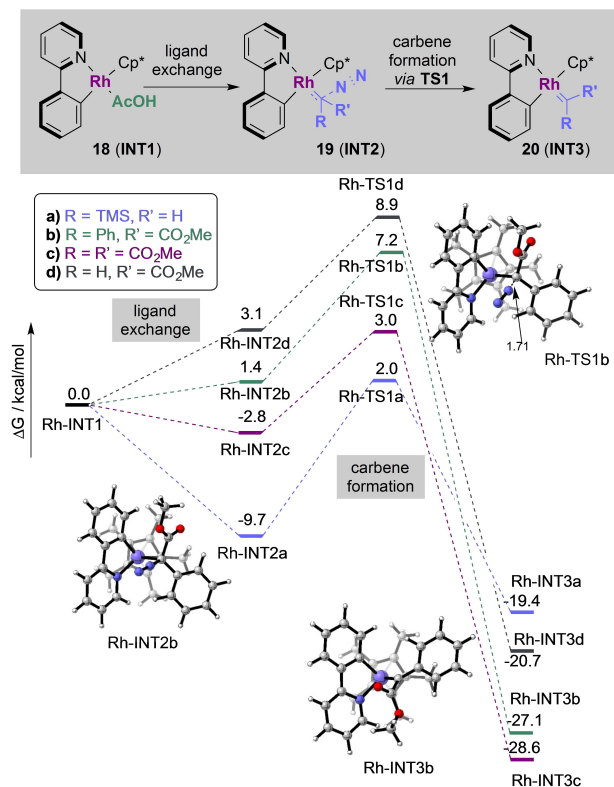
As reaction temperature, 80 °C was found to be optimal and both lower or higher temperatures led to a significant decrease yield of **12 a** (Table 1, entries 8,9). Moreover, we investigated a metal-free, blue light-mediated approach leading to the formation of only trace of the desired product (Table 1, entry 10). Finally, when increasing the addition time of TMS diazomethane (**10**) to 10 h to improve the yield of **12 a** to 91% without overreaction to the double C–H functionalization product (Table 1, entry 11).

In a next step, we aimed at the desilylation of **12 a** to directly achieve C–H methylation reactions and therefore studied the effect of TBAF·3H₂O. When adding TBAF·3H₂O directly at the beginning, a moderate yield of the C–H methylation product **13 a** was obtained (Table 1, entry 12). This yield could be significantly improved in a one-pot two-step approach by addition of TBAF·3H₂O after completion of the initial C–H alkylation of phenyl pyridine **9 a** with TMS diazomethane (**10**) (Table 1, entry 13). In this case, a high yield of the desired C–H methylation product was obtained. Importantly, other methods for desilylation proved inefficient and only a moderate yield of product **13 a** was obtained upon desilylation (Table 1, entries 14,15). Furthermore, we studied the use of simple MeI instead of **10** for the synthesis of **13 a**, yet we did not observe any product formation when adding four equivalents of MeI over 10 h (Table 1, entry 16).

With the optimized conditions in hand, we embarked on investigations on the applicability of this alkylation reaction. We first examined the methylation reaction of 2-aryl pyridine derivatives **9** employing the one-pot two-step protocol.

Different alkyl groups and halogens were tolerated in the *para*-position of the aryl group and selective mono-methylation occurred in good to high yield. *Meta*-substituted aryl groups underwent a selective C–H functionalization in the *para*-position to the existing *meta*-substituent. This observation can be reasoned by steric hindrance of the *meta*-substituent and a more facile C–H insertion step into the sterically less hindered C–H bond by the rhodium catalyst. When employing 2-(2-methyl phenyl)-pyridine, we observed the C–H functionalization product in reduced yield (53%). Further examples under investigation consist of different substitution patterns around the pyridine ring as well as electron-rich heterocycles or carbocycles, which smoothly underwent C–H functionalization reaction (Scheme 4a).

To further broaden the scope of this C–H alkylation reaction, we examined the reaction of TMS diazomethane without cleavage of the TMS group. We examined a comparable substrate scope for the introduction of the trimethylsilyl methylene group and consistently obtained slightly higher yields of the alkylation product in comparison to the methylation reaction, which we reason by the efficiency of the desilylation step (Scheme 4b).
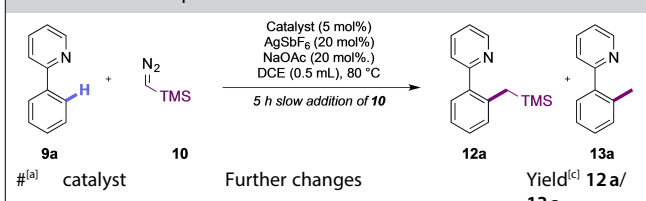
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Scheme 3. Theoretical studies on the rhodium-catalyzed reaction of different diazoalkanes with 2-phenyl pyridine. Calculations were performed at BP86-D3/6-311++G(d,p)/def2tzvpp// BP86-D3/6-31G(d,p)/SDD level.

Table 1. Reaction optimization.

#[a]	catalyst	Further changes	Yield[c] 12a/13a
1	[Cp*RhCl₂]₂	–	79/–
2	[Cp*IrCl₂]₂	–	*trace/–*
3	[Ru(cymene)Cl₂]₂	–	28/–
4[b]	[Cp*Co(CO)I₂]	–	*decomposition*
5	[Cp*RhCl₂]₂	no NaOAc	–/–
6	[Cp*RhCl₂]₂	KOAc instead of NaOAc	33/–
7]	[Cp*RhCl₂]₂	no AgSbF₆	*trace/–*
8	[Cp*RhCl₂]₂	120 °C	44/–
9	[Cp*RhCl₂]₂	40 °C	30/–
10	[Cp*RhCl₂]₂	30 °C, 470 nm LED	*trace/–*
11	[Cp*RhCl₂]₂	addition of **10** over 10 h	91/–
12	[Cp*RhCl₂]₂	plus TBAF·3H₂O	–/50
13	[Cp*RhCl₂]₂	Addition of TBAF·3H₂O (1.5 equiv.) after addition of **10**	–/86
14	[Cp*RhCl₂]₂	Addition of KOTMS (5 mol%), DMSO (0.4 mL) and H₂O (1.0 equiv.) after addition of **10**	–/12
15	[Cp*RhCl₂]₂	Addition of CsF (1.0 equiv.), 18-crown-6 (1.1 equiv.) and DMSO (0.5 mL) after addition of **10**	–/42
16	[Cp*RhCl₂]₂	Slow addition of MeI (4 equiv.) instead of **10**	*no product formation*

[a] *Reaction conditions*: 0.2 mmol of **9a** (1 equiv.), 5 mol-% catalyst, 20 mol% NaOAc and 20 mol% AgSbF₆ in 0.5 mL of dry, degassed 1,2-DCE. 0.8 mmol of **10** (2 M solution in hexane) plus 0.1 mL dry, degassed 1,2-DCE total volume is 0.5 mL was added to the reaction mixture over 5 h and stirred at 80 °C. [b] 10 mol% [Cp*Co(CO)I₂] was used. [c] Isolated yield.

Last, we embarked on studies of further diazoalkane reaction partners. In particular, we became interested in the C–H functionalization reaction with donor/acceptor diazoalkanes. The latter have a long tradition in C–H functionalization reactions of C–H bonds using different metal catalysts. However, the majority of approaches rely on catalyst-controlled C–H functionalization reactions or on the intrinsic reactivity of C–H bonds to control the reaction outcome. On the contrary, directing groups to exhibit a control on the site of C–H functionalization reaction are much less commonly employed and typically thermally-stable acceptor-type diazoalkanes are employed owing to the forcing reaction conditions. To the best of our knowledge, there are only two reports using either cobalt- or rhodium-based catalysts for directing group-assisted C–H functionalization reactions with donor/acceptor diazoalkanes, however rapid intramolecular amide formation occurs and prevents isolation of the C–H functionalization product.[10] Furthermore, there is one study on the cobalt-catalyzed C–H functionalization of 1-(pyridine-2-yl)-1H-indole and 1-aryl-1H-pyrazoles.[11]

Against this background, we were delighted to observe that after brief optimization (for details, please see Table S2 in Supporting Information), we could identify conditions to conduct such C–H functionalization reaction with high efficiency. Here, different substitution patterns on the aromatic ring and ester groups of the donor/acceptor diazoalkane were well-tolerated to afford the C–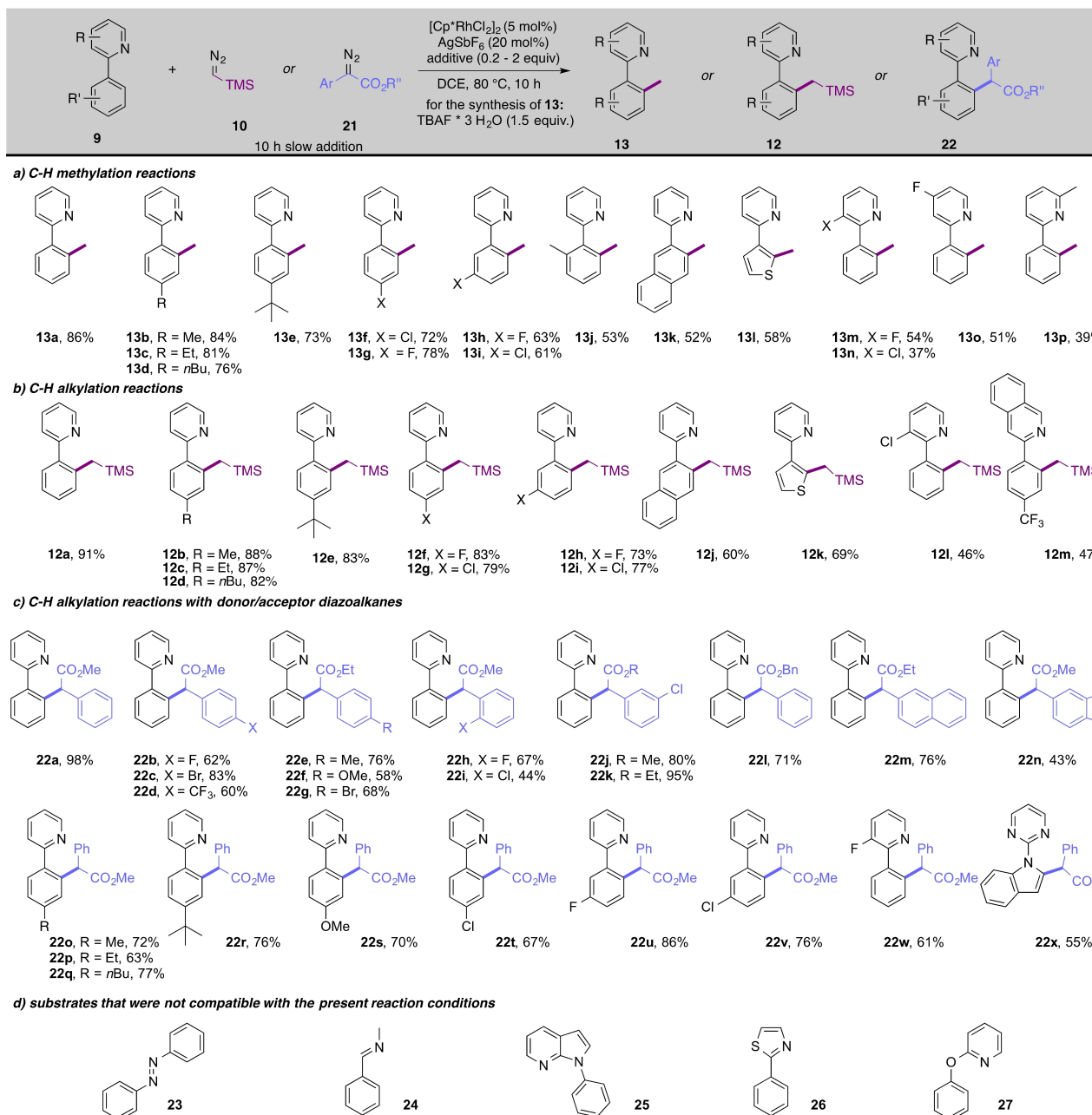H functionalization products in high yields. As in the C–H methylation reaction, this C–H alkylation reaction proved tolerant over a range of different substituents on the 2-aryl pyridine substrate, bearing alkyl groups or halogens around the aromatic ring and the pyridine ring. Interestingly 1-(pyrimidin-2-yl)-1H-indole was also compatible with the present reaction conditions and we were able to isolate the C–H functionalization product in good yield (Scheme 4c).

Furthermore, we investigated different directing groups, such as (E)-1,2-diphenyldiazene (**23**), imine **24**, 1-phenyl-1H-pyrrolo[2,3-b]pyridine (**25**), 2-phenylthiazole (**26**), or 2-phenoxypyridine (**27**), while none of the directing groups investigated was compatible with the present reaction conditions. In all cases, no product formation was observed and **10** or **21** decomposed (Scheme 4d).

In addition to our computational calculations, we performed control experiments with preformed complex **28** in the reaction with TMS diazomethane. When using complex **28** in stochiometric amounts and four equivalents of TMS diazomethane (**10**), we were surprised to identify the double C–H functionalized product in 81% yield. In a second step, we investigated the reaction using stoichiometric amounts of [Cp*RhCl₂]₂ and identified the double C–H functionalized product in 64%, while we also detected the mono C–H functionalization product in
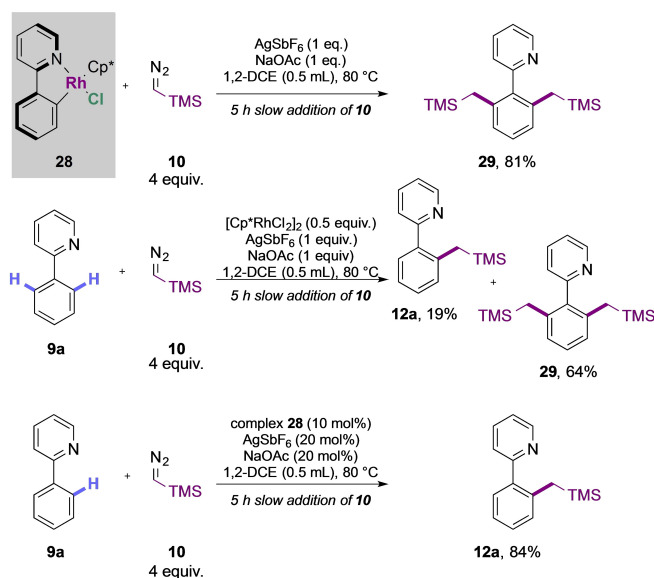
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Scheme 4. Substrate scope of a) C–H methylation reactions; b) C–H alkylation reactions; c) C–H alkylation reactions with donor/acceptor diazoalkanes; and d) substrates that were not compatible with the present reaction conditions.

19% yield. The formation of **29** in stoichiometric reactions might be related to reduced ligand exchange due to low concentrations of unbound 2-phenyl pyridine in the reaction mixture.

Furthermore, we investigated preformed complex **28** in catalytic amounts and observed the mono C–H functionalized product in 84% yield, which is similar to the reaction of [Cp*RhCl₂]₂ instead to complex **28** (Scheme 5). This observation points at the catalytic activity of preformed complex **28** in the reaction.

Conclusion

The thermal C–H methylation and alkylation reaction of 2-aryl pyridines with TMS diazomethane and donor/acceptor diazoalkanes was reported. Initial computational calculations suggested that Rh-salts are suitable catalysts for a broad variety of different diazoalkanes and after a short optimization, conditions that allow the selective C–H methylation with TMS diazomethane were identified. This approach is compatible with a broad variety of substituted 2-phenyl pyridines including *ortho*-substituted ones. Notably, only the formation of the mono C–H

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Scheme 5. Control experiments with preformed complex.

functionalization reaction product was observed. Moreover, we could further showcase the expansion of this methodology towards alkylation reactions with donor/acceptor diazoalkanes.

Experimental Section

General information: Unless otherwise noted, all commercially available compounds were used as provided without further purification. Solvents used in reactions were p.A. grade. Solvents for chromatography were technical grade and distilled prior to use. Analytical thin-layer chromatography (TLC) was performed on Macherey–Nagel silica gel aluminum plates with F-254 indicator, visualized by irradiation with UV light. Column chromatography was performed using silica gel Merck 60 (particle size 0.063–0.2 mm). Solvent mixtures are understood as volume/volume. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR were recorded on a Varian AV600/AV400 or an Agilent DD2 400 NMR spectrometer in CDCl$_3$. Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated br (broadened singlet), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (J) are in Hertz (Hz). HRMS data were recorded on a ThermoFisher Scientific LTQ Orbitrap XL using ESI ionization or on a Finnigan MAT 95 using EI ionization at 70 eV. IR spectra were recorded on a Perkin Elmer 100 spectrometer and are reported in terms of frequency of absorption (cm^{-1}).

Important safety note!!! Handling of diazo compounds should only be done in a well-ventilated fume cupboard using an additional blast shield. No incidents occurred handling of diazoalkanes during the preparation of this manuscript, yet the reader should be aware of carcinogenicity and explosiveness of the herein described diazo compounds. General safety precautions when working with diazomethane and its derivatives should be followed. Any reactions described in this manuscript should not be performed without strict risk assessment and proper safety precautions.

General procedure for methylation reactions: An oven-dried test tube was loaded with [Cp*RhCl$_2$]$_2$ (6.18 mg, 5 mol%), AgSbF$_6$ (13.7 mg, 20 mol%), NaOAc (3.28 mg, 20 mol%) and corresponding

2-phenylpyridiene **9** (0.2 mmol, 1 equiv., if solid). The test tube was flushed and refilled with argon for three times. Then dry, degassed 1,2-DCE (0.5 mL) and the corresponding 2-phenylpyridiene **9** (0.2 mmol, 1 equiv., if liquid) were injected into the reaction tube with the back flow of argon. In a second test tube, trimethylsilyl diazomethane **10** (2 M solution in hexane – 0.4 mL, 0.8 mmol, 4.0 equiv.) and dry, degassed 1,2-DCE (0.1 mL) were added. The resulting solution of trimethylsilyl diazomethane **10** was added slowly to the rection mixture heated to 80 °C over 10 h. After the addition was finished the resulting reaction mixture was cooled down to room temperature. TBAF·3 H$_2$O (126 mg, 0.4 mmol, 2 equiv.) was added to the reaction mixture and stirred at room temperature for 2 h. Finally the reaction mixture was diluted with DCM and the product was purified by silica column chromatography using n-hexane : ethyl acetate as eluent to afford the corresponding methylated product.

General procedure for C−H alkylation reactions: An oven-dried test tube was loaded with [Cp*RhCl$_2$]$_2$ (6.18 mg, 5 mol%), AgSbF$_6$ (13.7 mg, 20 mol%), NaOAc (3.28 mg, 20 mol%) and corresponding 2-phenylpyridiene **9** (0.2 mmol, 1 equiv., if solid). The test tube was flushed and refilled with argon for three times. Then dry, degassed 1,2-DCE (0.5 mL) and the corresponding 2-phenylpyridiene **9** (0.2 mmol, 1 equiv., if liquid) were injected into the reaction tube with the back flow of argon. In a second test tube, trimethylsilyl diazomethane **10** (2 M solution in hexane – 0.4 mL, 0.8 mmol, 4.0 equiv.) and dry, degassed 1,2-DCE (0.1 mL) were added. The resulting solution of trimethylsilyl diazomethane **10** was added slowly to the rection mixture heated to 80 °C over 10 h. After the addition was finished the resulting reaction mixture was cooled down to room temperature and diluted with DCM and the product was purified by silica column chromatography using n-hexane : ethyl acetate as eluent to afford the corresponding alkylated product.

General procedure for C−H alkylation reactions with donor/acceptor diazoalkanes: An oven-dried test tube was loaded with [Cp*RhCl$_2$]$_2$ (5 mol%, 6.8 mg), AgSbF$_6$ (20 mol%, 13.7 mg), and KOAc (0.3 mmol, 1.5 equiv., 29.4 mg). The test tube was flushed and refilled with Ar for three times. Then dry, degassed 1,2-DCE (0.5 mL) and the corresponding 2-phenylpyridiene **9** (0.4 mmol, 2 equiv.) were added. In a second test tube, diazoalkane **21** (0.2 mmol, 1.0 equiv.) was dissolved in dry, degassed 1,2-DCE (0.5 mL). The resulting solution of diazoalkane was added slowly to the rection mixture heated to 80 °C over 5 h. After the addition was finished the resulting reaction mixture was stirred for another 5 h at 80 °C. The product was purified by silica column chromatography using n-hexane : ethyl acetate as eluent.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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