EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202300759

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2-(*o*-Tolyl) Pyridine as Ligand Improves the Efficiency in Ketone Directed *ortho*-Arylation

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Herein, we report a ruthenium-catalyzed ketone directed *ortho*-arylation wherein the addition of a bidentate NC-type ligand, most effectively 2-(o-tolyl) pyridine, significantly enhances the C–H arylation reaction. Various aryl-alkyl ketones, including cyclic, aliphatic, and heterocyclic ones, are competent substrates, and arylboronic acid esters were used as aryl sources. However, substitution with OMe and CF_3 in the aromatic ring of the ketone substrates is not tolerated, while such residues on the benzoic ester are possible. Notably, this study provides valuable insights into ketone-directed ortho arylation in the presence of 2-(o-tolyl) pyridine and adds additional options for catalyst and ligand optimization in ruthenium-catalyzed C–H functionalization.

Introduction

Transition metal-catalyzed C–H bond functionalization is of continuing interest due to its remarkable versatility in modifying organic frameworks and potentially reducing synthetic steps towards target molecules.[1] However, C–H bonds are ubiquitous in organic compounds, making selective manipulation of a specific C–H bond within complex molecules a challenge. One of the most effective strategies to achieve regioselectivity in C–H functionalization is through the use of directing groups.[2] Directing groups are functional moieties that can be natively or temporarily attached to a molecule, guiding the transition metal catalyst to selectively activate a particular C–H bond. Strongly coordinating nitrogen, phosphorus, and sulfur-based functional groups (FGs) are frequently utilized as directing groups (DGs). However, even weaker coordinating functional groups can be competent DGs. Specifically, ketones are attractive DGs as they can be transformed subsequently into a diverse range of functional groups and are frequently present in bioactive molecules and functional materials.[3] Hence, in the frame of an investigation towards selective C–H functionalization in the presence of multiple directing groups, ketone-directed arylation was selected as one of the model reactions. Such ketone-directed ortho-arylations for the synthesis of biaryl systems have been established previously, e.g., by the groups of Miura,[4] Kakiuchi,[5] Rao,[6] and Lu and Sun.[7] Additionally, Chatani's group demonstrated base-free *ortho*-C–H arylation under mild conditions[8] (Scheme 1A). However, there are limitations to implementing these protocols in the presence of other directing groups. Complex molecules usually contain multiple functional groups that can exhibit directing effects, and there are only a few literature studies that compare the efficiency of directing groups in the presence of multiple directing groups.[9] A second DG frequently applied in direct C–H functionalization is pyridine. There is literature precedent showing that ruthenium can form a cyclometallated complex through coordination with the 2-phenyl pyridine substrate as a key intermediate for its C–H arylation reaction.[10] In this context, research conducted by Ackermann on direct arylation with a Ru^{II} carboxylate catalyst illustrates the formation of a mono-cyclometallated complex under typical reaction conditions.[11] Furthermore, it has been observed that these complexes serve as effective pre-catalysts, as depicted in Scheme 1B. In 2011, Dixneuf conducted mechanistic investigations that revealed an autocatalytic process in the Ru^{II}-catalyzed arylation of arenes. These findings suggest that the conversion of a $Ru(OAc)_2$(*p*-cymene) precatalyst into a cyclometallated species is a facile process.[12] Nevertheless, early research from 2007 suggested that Ru-catalysts lacking a p-cymene are similarly good catalysts for C–H activation.[13] Larrosa's study on ruthenium-catalyzed late-stage arylations shed light on *p*-cymene free cyclometallated ruthenium complexes (Scheme 1B).[14] The *p*-cymene ligand inhibited the reaction, and high reaction temperatures were needed only to dissociate it from the ruthenium core. After *p*-cymene ligand dissociation, the reaction rate increases. These results led to the creation of a mono-cyclometallated precatalyst **[Ru1]** in Scheme 1B without η6-arene ligands. This novel catalyst enabled C–H arylation at much milder conditions. Furthermore, they showed in Scheme 1B that a bis-cyclometallated ruthenium intermediate **[Ru2]** is necessary for oxidative addition of aryl halides. Following Larrossa's pioneering work, Ackermann and Greaney showed that *p*-cymene from

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202300759

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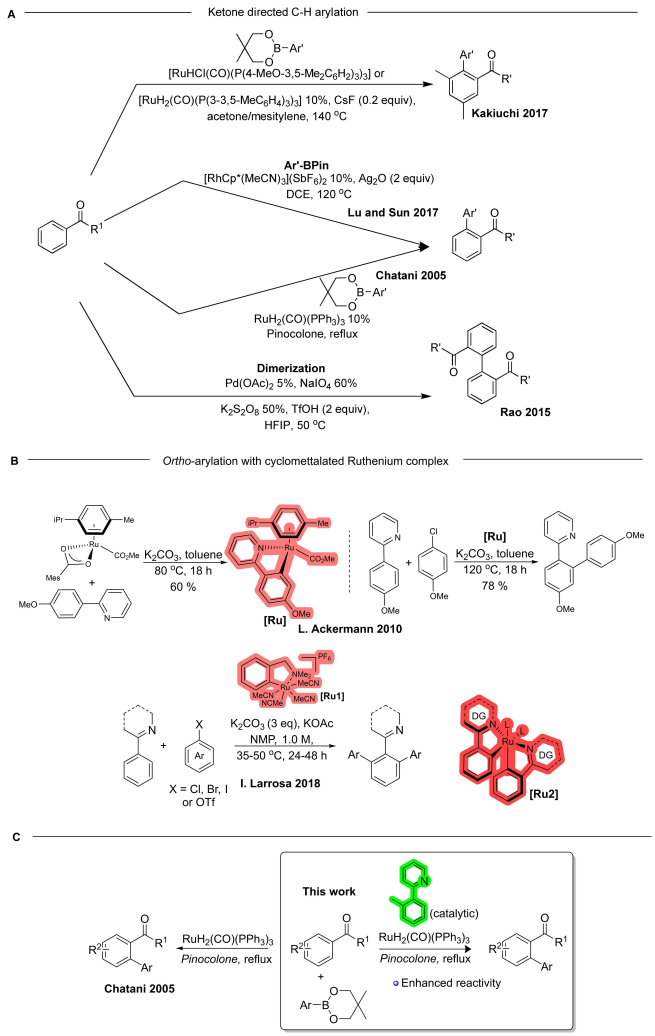

Scheme 1. A) Previous work on ketone directed C–H arylation, B) Previous work on *ortho*-arylation with cyclometallated ruthenium complex, C) Current work.

$[RuCl_2(p\text{-cymene})]_2$ precatalyst can be irradiated with visible light to form an in situ *p*-cymene free active catalyst that can promote C–H arylation at room temperature.[15]

Within this paper, we will present new opportunities for the preparation of biaryl compounds using DG-assisted C–H functionalization, with a particular emphasis on ketone-directed ortho C–H arylation. In addition, we demonstrate that 2-aryl pyridines in catalytic amounts can improve the efficiency in the aforementioned transformation eventually opening new opportunities to optimize C–H functionalization with other DGs as well.

Results and Discussion

The initial aim of the project was to selectively exploit the directing ability of one specific DG in the presence of another. Originally, two frequently applied DGs were selected, namely ketone and pyridine. In a first step, individual reaction conditions for either ketone or pyridine were applied, based on literature precedence, before competition experiments were carried out. This is a challenging pair of DGs for the development of orthogonal reaction conditions, which is highlighted by the fact that conditions originally developed for ketone directed arylation[7] proved to be effective for pyridine directed arylation as well in our hands giving product **5a** in 58% yield (Figure 1. Conditions B). Another protocol for ketone-directed arylation was based on the method outlined by Chatani and co-workers.[8] However, in our hands, we obtained the desired product **3a** with a yield of only 30%, which was significantly lower compared to the literature's yield of 76% of **3a** (Figure 1. Conditions A). From experience, we know that the source and batch of catalyst can have a significant impact on the success of a reaction, and even though we tried catalyst batches from several suppliers (and carefully checked the qualities of all other components of the reaction mixture), it cannot be excluded that this is the reason for the significant discrepancy.

Hence, we moved on and carried out a first competition experiment. A 1:1 mixture of substrates **1a** and **L1** was subjected to reaction conditions B, which led to exclusive ortho-arylation of **L1**, giving **5a** in 40% yield in this first try. Surprisingly, when carrying out the second competition experiment, namely applying conditions A to the same mixture of starting materials **1a** and **L1**, neither **3a** nor **5b** were obtained in appreciable amounts.

It was hypothesized that the pyridine directing group could act as a strong ligand for the applied Ru complex, leading to a catalytically inactive species when a full equivalent of **L1** is present. To validate this hypothesis, **L1** was added in lower concentrations, which should restore some catalytic activity, at least at concentrations below the one for the Ru-complex. Surprisingly, in these control experiments, we observed even improved reactivity when 0.05 to 0.1 equivalents of **L1** were applied (Table 1, Entries 2–3). In these two cases, 60% of **3b**

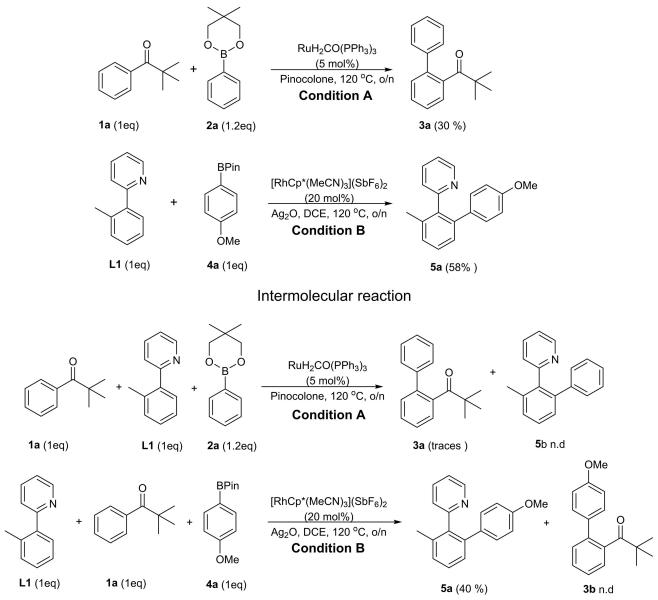

Figure 1. Preliminary reaction conditions.

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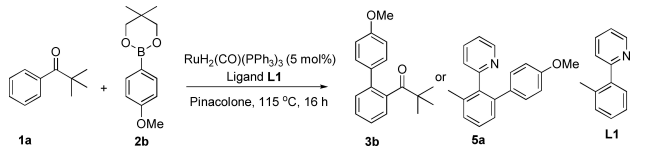
Table 1. Test of ligand hypothesis.[a]



Entry	Ligand L1 [eq]	**3b** Yield [%]	**5a** Yield [%][b]
1	–	25	–
2	0.05	60	3
3	0.1	68	7
4	0.3	40	15
5	0.5	29	5
6	1.0	traces	–

[a] Reaction conditions: **1a** (0.2 mmol), ligand (**L1**), $RuH_2(CO)(PPh_3)_3$, pinacolone (0.3 mL), 16 h. Yields indicated are yields of isolated product. [b] GC-MS yield.

was obtained with 0.05 equiv. **L1**, whereas 0.1 equiv. even delivered 68% of **3b** accompanied by small amounts of **5b**, the arylation product of **L1**. Obviously, the presence of **L1** in a catalytic amount not only restored, but even increased the catalyst activity, leading to higher yields. Further increasing the amount of **L1** led again to a decrease in yield, with only trace amounts of **3b** being formed in the presence of a full equivalent of **L1** (Table 1, Entries 4–6).

It was hypothesized that **L1** forms a new complex with Ru in situ, which shows better performance in the investigated transformation. From the results listed in Table 1, a Ru-complex with either one or two **L1** ligands was expected to be the species of interest. Before trying to identify the respective species, it was tested whether other ligands with similar features as **L1** might display a similar or even better positive effect. Ligands **L2**–**L11** were chosen to determine important features of the supporting ligand (Figure 2). With ligands **L2** and **L3**, it was tested, whether an o-methyl group is required. The corresponding experiments delivered **3b** in 15% and 38% yields, respectively, indicating that the CH_3 group was an important feature. When testing ligand **L4**, which has two o-methyl groups, **3b** was obtained in a decreased yield of 27%, which is in the range of the original "ligand-less" conditions. It is likely that bulky **L4** does not coordinate at all with Ru under these conditions since in contrast to **L1**, which can act as bidentate C–N ligand, **L4** does not have this possibility. To explore this further, we tested ligands **L5** and **L6**. Ligand **L5** yielded only 1% of the desired product, suggesting that **L5** is coordinating too strongly via an N–N binding mode, leading to an inactive catalyst. **L6** gave again 27% yield, which is similar to the experiment without ligand. As a monodentate ligand, it will be weaker coordinating and likely not be able to substitute neither CO nor PPh_3 of the original complex. We also investigated whether a 6,6-membered system was necessary for the ligands. For that, we tested ligands **L7**–**L11**. Ligand **L7** was almost as effective as ligand **L1**, yielding 60% of the desired product. Interestingly, **L8**, which can be considered as the

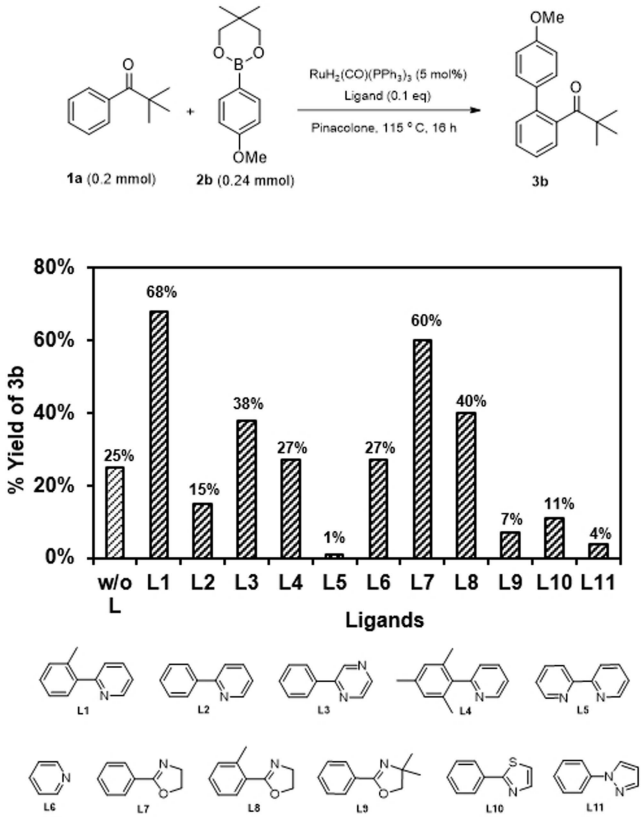


Figure 2. Ligand scope.

oxazoline derivative of **L1**, was found to have a significantly lower beneficial effect as compared to **L7**, with a yield of 40% in the respective experiment. This may be due to the difference in geometry when moving from a 6-membered to a 5-membered ring, where the CH_3 group points in a different direction. Ligands **L9**, **L10**, and **L11** were found to be unsuitable candidates, yielding 7%, 11%, and 4% of the desired product, respectively. Overall, our ligand screening demonstrated the importance of the o-methyl group and the bidentate binding mode via N and C.

Finally, a short reaction optimization was carried out (see supporting information Table 2 for details). At 80 °C the reaction rate dropped and after 6 h 44% of desired product **3b** were obtained. Lowering the catalyst amount to 2 mol% or increasing it to 10 mol% again decreased the yield.

As mentioned previously, we could not reproduce the yield reported in the literature for the synthesis of **3a** (30%) (76% in Chatani's work)[8] (yields mentioned are under condition A, Figure 1). It has to be mentioned again that the source and batch of catalyst can have a significant impact on the success of a reaction, which could be an explanation for the differences in yield. In this light, it is especially interesting that the addition of an external ligand seems to improve catalytic activity. Having the optimized reaction conditions in hand, we examined the reaction scope (Table 2). Compound **3b** was obtained monoselectively in 68% yield. Interestingly, already a small decrease in the steric bulk of the ketone directing group led to mixtures

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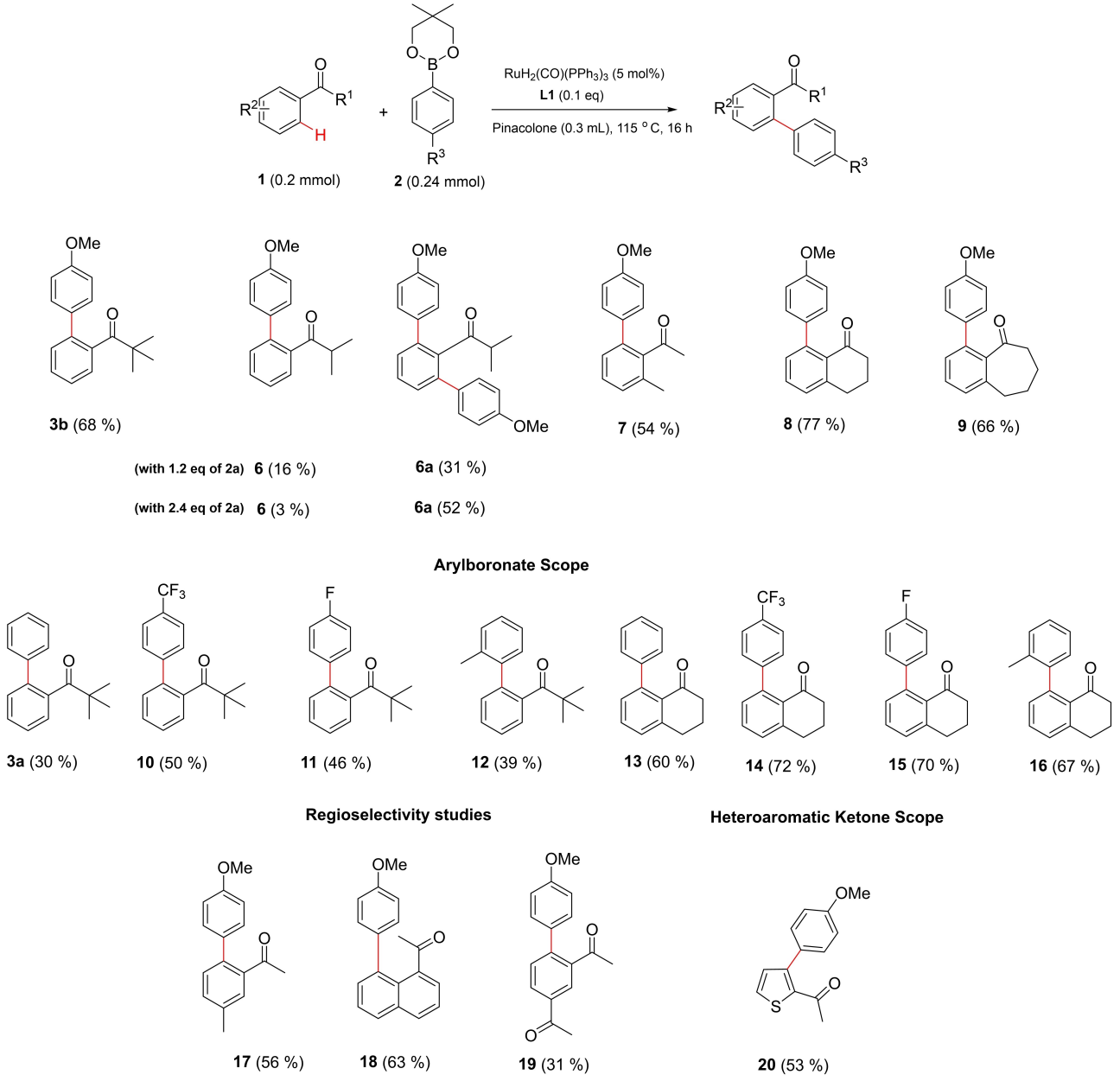
Table 2. Reaction scope.[b]



[b] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol) ligand **L1** (0.1 equiv.), $RuH_2(CO)(PPh_3)_3$, pinacolone (0.3 mL), 16 h. Yields indicated are yields of isolated product.

of mono- and bis-arylated products. When 1.2 equiv. of boronic acid ester were applied with the less-hindered isobutyl-ketone, the diarylated product was already favored in a ratio of ~1:2 mono:bis. Increasing the amount of the arylating agent to 2.4 equiv. The diarylated product was formed almost exclusively (~1:17 mono:bis). Also, an acetyl DG gave the corresponding product **7** (54%) and cyclic ketones are suitable starting materials as well, giving the arylated products **8** (77%) and **9** (66%) in good yields. This shows that various ketones can promote this transformation. However, substitutions such as methoxy and trifluoromethane at the ortho, meta, or para positions of the directing group did not give the desired product (see supporting information Scheme S1). Only a methyl group was tolerated (vide infra). In contrast, functional groups on the boronate coupling partner are tolerated.

Various substituted arylboronates **2a** and **2c**–**2e** reacted effectively with the aromatic ketones **1a** and **1d** affording the corresponding arylated compounds **3a**, **10**–**12** and **13**–**16**. Here it was observed that the cyclized ketone substrate tetralone generally gave significantly better yields, suggesting that a rigid substrate is beneficial. Next, we examined the scope of the regioselectivity of the reaction. Unsymmetrical **1f** with two

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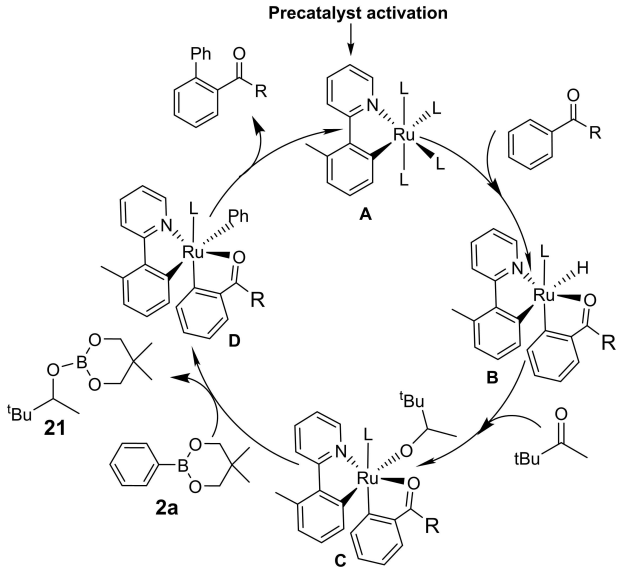
ortho C–H bonds available for arylation afforded **17** (56%) in a highly regioselective manner, with arylation occurring at the less sterically hindered C–H bond. The arylation of methyl-1-naphthyl ketone occurred exclusively in position 8 rather than in position 2 (**18**, 63%). On 1,3-diacetylbenzene as substrate, the arylation occurred on the sterically more favourable side and not in between the two DGs, but in a lower yield of **19** (31%). No diarylated product was observed in this case. Finally, 2-acetylthiophen was tested as a heterocyclic substrate, and the corresponding arylation product **20** was obtained in 53% yield.

Drawing from previous research on cyclometalated ruthenium complexes,[10] as well as Chatani's work on ruthenium catalyzed C–H arylation,[6] and our own observations, a mechanism is proposed (Scheme 2). Initially, activation of the pre-catalyst $RuH_2(CO)(PPh_3)_3$ leads to the generation of a monocyclometallated intermediate **A**. This is followed by C–H activation of the ketone-directing group, resulting in the formation of bis-cyclometalated complex **B**. Furthermore, the addition of the Ru–H bond to the carbonyl group of pinacolone leads to the formation of an intermediate **C**. Subsequently, transmetalation between intermediate **C** and **2a** affords intermediate **D** and trialkoxyborane **21**. Reductive elimination takes place preferentially between the weaker ligand, the corresponding aryl-ketone, and the aryl residue giving the arylated ketone products.

Referring to Table 1, it was observed that as side product **5a** was formed as well when applying **L1** in amounts between 0.05 to 0.5 equivalents (Table 1, Entries 2–5). A yield of 3% for **5a** was obtained with 0.05 equiv. **L1**, whereas an increase to 0.3 equiv. resulted in a yield of 15% for **5a**. However, further increasing the amount of **L1** to 0.5 equiv. led again to a decrease in side product **5a**. Notably, in the presence of a full equivalent of **L1**, no **5a** was formed (Table 1, Entry 6). This indicates that the intermediate **A** has the ability to coordinate with a second unit of **L1** instead of ketone, which can then undergo C–H activation and reductive elimination to generate coupling product **5a**, up to a certain concentration range (0.05 to 0.3 equiv. of **L1**). However, further increasing the amount of **L1** may result in the formation of an intermediate complex where three **L1** molecules can be coordinated to the Ru metal, rendering it inactive. When 1 equiv. of **L1** was subjected to the reaction conditions in presence of 1 equiv. of $RuH_2(CO)(PPh_3)_3$ the complex [**Ru3**] could be isolated (see supporting information Scheme S2), containing one 2-toulyl-pyridine ligand, two PPh_3 units and one CO ligand. Subjecting this complex to the optimized reaction conditions in presence of substrates **1a** and **2b**, no product formation was observed. [**Ru3**] is eventually a relatively stable complex not involved in the catalytic cycle at all, or formed in a catalyst deactivation pathway.



Scheme 2. Proposed mechanism.

Conclusions

In summary, the utilization of 2-(o-tolyl) pyridine as a ligand in Ru-catalyzed ketone-directed ortho arylation reactions has proven to be an effective strategy for enhancing the overall efficiency of the process. Important structural features of the ligand were identified (o-tolyl, bidentate binding mode via N and C). Various combinations of aromatic ketones (e.g., acetophenones, fused-aromatic ketones, and heteroaromatic ketones) and arylboronates are good candidates for this arylation. Among ketones, fused aromatic ketones such as alpha-tetralones exhibited a high degree of reactivity. Nevertheless, the intended product was not observed when methoxy and trifluoromethane were substituted in the ortho, meta, or para positions of the directing group. So far, isolation of the catalytically active species has not been successful. It is important to note that further studies are required to fully elucidate the underlying mechanistic details of the ligand's effect on the reaction and explore its applicability to different substrates and metal catalyst systems, which are in progress.

Experimental Section

Chemicals were purchased from commercial suppliers. Aliphatic and aromatic ketones were distilled over $CaSO_4$. All reactions were magnetically stirred and heated in a metallic reaction block in an 8 mL Teflon-capped vial. Purification was accomplished using preparative thin layer chromatography on 20×20 cm^2 silica gel plates (layer thickness 1,000 μm). NMR-spectra were recorded in $CDCl_3$ on Bruker Avance UltraShield 400 spectrometer, and chemical shifts (δ) are reported in ppm and are referenced to the solvent peak. For $CDCl_3$, proton NMR spectra were referenced to 7.26 ppm and carbon NMR spectra to 77.16 ppm respectively. Coupling constants (J) are given in Hertz (Hz). Multiplicities of the signals are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, ddd = doublet of doublet of doublet and bs = broad singlet. Carbon NMR were as standard decoupled ^{13}C-spectra. GC–MS runs were performed on a Thermo Finnigan Focus GC/DSQ II using a standard capillary column BGB 5 (30 m×0.32 mm ID). GC spectra were recorded on a Thermo Focus GC using a BGB-5 capillary column (30 m×0.32 mm, 1.0 μm film, achiral) with the following oven temperature program: Start at 100 °C (hold 2 min), 35 °C/min, 300 °C (hold 4 min). HR-MS for

literature unknown compounds were carried out at TU Wien, Institute for Chemical Technologies and Analytics; all samples were analyzed by LC-IT-TOF-MS in only positive ion detection mode with the recording of MS and MS/MS spectra. All samples were filtered through PALL Acrodisc CR 13 mm syringe filters with 0.2 μm PTFE membrane prior to GC analysis. MALDI experiments were carried out at TU Wien, Institute for Chemical Technologies and Analytics. The freeware tool IsoPro 3.0 calculates all isotopic clusters for MALDI at a resolution of 10.000 (FWHM). As ruthenium has a rather broad isotope distribution (7 isotopes over 10 Da), as molecular mass the Ru-isotope with the highest abundance was chosen (i.e., ^{102}Ru) for calculation of the molecular masses.

General procedure for the ketone directed C-H ortho arylation

An 8 mL glass vial was filled with the respective ketone substrate (0.2 mmol, 1 equiv.), boronic ester (0.24 mmol, 1.2 equiv.), ligand (0.1 mmol) and $RuH_2(CO)(PPh_3)_3$ (5 mol%) inside a glove box. Pinacolone (0.3 mL) was added to the reaction mixture. The reaction mixture was stirred at 115 °C for 16 h. The progress of the reaction was monitored by GC-MS. The crude residue was purified by preparative thin layer chromatography on 20×20 cm silica gel plates (layer thickness 1000 μm), PE: EtOAc (2 : 1).

Supporting Information

The authors have cited additional references within the Supporting Information (Ref. [16–23]).

Acknowledgements

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie, Grant Agreement No 860762. The authors acknowledge TU Wien Bibliothek for financial support through its Open Access Funding Programme.

Conflict of Interests

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.

Keywords: C–H activation · Ketone directed *ortho*-arylation · Ligand · Directing group · Cyclometallated complex

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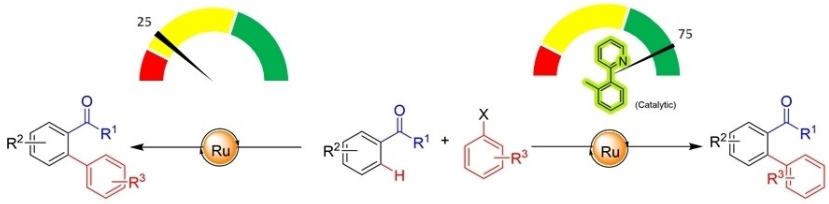
Manuscript received: July 27, 2023
Revised manuscript received: September 11, 2023
Accepted manuscript online: September 14, 2023
Version of record online: ■■, ■■



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2-(*o*-Tolyl) Pyridine as Ligand Improves the Efficiency in Ketone Directed *ortho*-Arylation

In this work, we explore how adding a catalytic amount of an NC-type ligand improves ketone-directed *ortho* C–H arylation, whereas a full equivalent shuts down the transformation. Increased catalytic activity stems from the formation of a cyclometallated complex containing the NC-type ligand to provide an intermediate which accelerates the ortho-arylation of the ketone substrate.