Nickel Catalysis Hot Paper

How to cite:
International Edition: doi.org/10.1002/anie.202103327
German Edition: doi.org/10.1002/ange.202103327

Direct Synthesis of Ketones from Methyl Esters by Nickel-Catalyzed Suzuki–Miyaura Coupling

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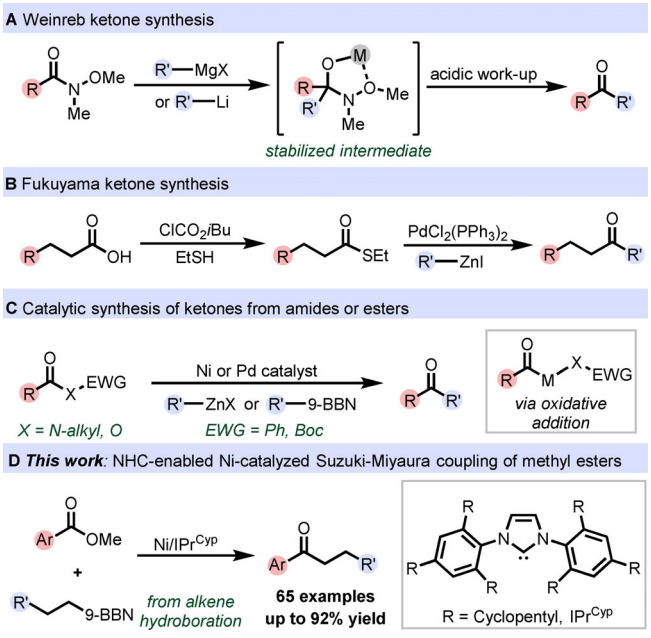
Abstract: *The direct conversion of alkyl esters to ketones has been hindered by the sluggish reactivity of the starting materials and the susceptibility of the product towards subsequent nucleophilic attack. We have now achieved a cross-coupling approach to this transformation using nickel, a bulky N-heterocyclic carbene ligand, and alkyl organoboron coupling partners. 65 alkyl ketones bearing diverse functional groups and heterocyclic scaffolds have been synthesized with this method. Catalyst-controlled chemoselectivity is observed for C(acyl)–O bond activation of multi-functional substrates bearing other bonds prone to cleavage by Ni, including aryl ether, aryl fluoride, and N-Ph amide functional groups. Density functional theory calculations provide mechanistic support for a Ni^0/Ni^{II} catalytic cycle and demonstrate how stabilizing non-covalent interactions between the bulky catalyst and substrate are critical for the reaction's success.*

Introduction

Transition-metal-catalyzed cross-coupling reactions are widely used in organic and medicinal chemistry to construct carbon-carbon and carbon-heteroatom bonds.[1] While traditional electrophilic coupling partners such as aryl bromides and iodides are most commonly used,[2] this has expanded recently to include a range of strong carbon-heteroatom bond activations.[3] For instance, cleavage of C–O bonds can enable the use of abundant phenol derivatives to synthesize diverse C(aryl) linkages in catalytic arylation, alkylation, and amination reactions.[4] Similar progress has been made in the use of carboxylic acid derivatives as cross-coupling electrophiles.[5] When the carbonyl group is retained in these reactions, C(acyl) linkages can be directly obtained, providing a valuable alternative to traditional acyl substitution reactions.

Ketones are among the most valuable targets in the cross-coupling of carboxylic acid derivatives due to the challenges associated with related stoichiometric acyl substitution reactions. For instance, aggressive organometallic nucleophiles such as Grignard reagents can directly attack carboxylic acid derivatives; however, the resultant ketones are prone to subsequent addition.[6] Prior derivatization of the substrate is generally needed to control this reaction, for instance by using the Weinreb ketone synthesis protocol (Scheme 1a).[7] In contrast, cross-coupling approaches use a transition metal catalyst to activate the acyl group, enabling milder organometallic nucleophiles to participate in the catalytic reaction while remaining inert to ketone products. For instance, the seminal works of Stille and Migita on the use of organotin nucleophiles in cross-coupling demonstrated the synthesis of ketones from acid chlorides.[8] Another milestone was reached in 1998 by the Fukuyama group who found Pd catalysts could activate thioesters towards coupling with organozinc nucleophiles (Scheme 1b).[9] Further expansion on the diversity of coupling partners and catalysts that participate in this type of reactivity continues to progress.[10]



Scheme 1. Strategies for the conversion of carboxylic acid derivatives to ketones.

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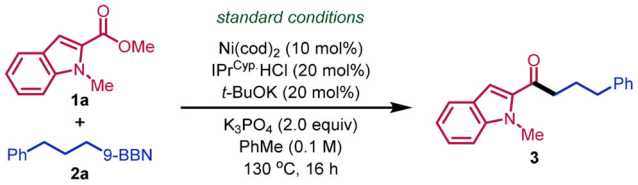
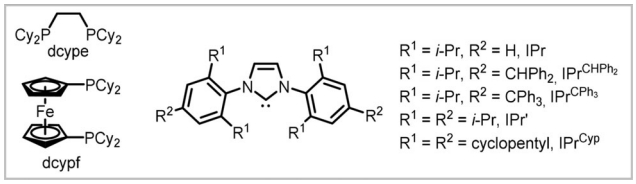
Most recently, amides[11] and esters[12] have been proven to be viable cross-coupling electrophiles. For example, towards accessing aryl alkyl ketones, Negishi- and Suzuki–Miyaura-type coupling reactions have been reported with activated amides[13] and phenyl esters[14] (Scheme 1c). While these acyl ester electrophiles are certainly more robust than acid chlorides, they are seldom commercially available and must be synthesized prior to coupling. In contrast, simple methyl and ethyl esters are abundant and make ideal starting materials; however, the relatively strong C(acyl)–O bond which lends them their stability also makes them more resistant to cleavage by transition metal catalysts.

The first report of the direct cross-coupling of unactivated esters was in 2016 when Garg and Houk described amide bond formation from 1-methyl naphthoates using stoichiometric Al(O*t*Bu)$_3$ and catalytic Ni.[15] Since then, only modest progress has been made in expanding the coupling of methyl esters to include more diverse coupling reactions, hindered by the limited catalysts available for cleaving the strong C–O bond.[16–20] Given the need for improved methods to access ketones from readily available carboxylic acid derivatives, we felt that the Suzuki–Miyaura cross-coupling of simple esters was a particularly important goal (Scheme 1d). Herein, we describe our endeavors in enabling this reaction using a Ni catalyst, an unusual NHC ligand with remote steric bulk, and alkylborane nucleophiles.

Table 1: Optimizing the Suzuki–Miyaura coupling of a methyl ester.[a]



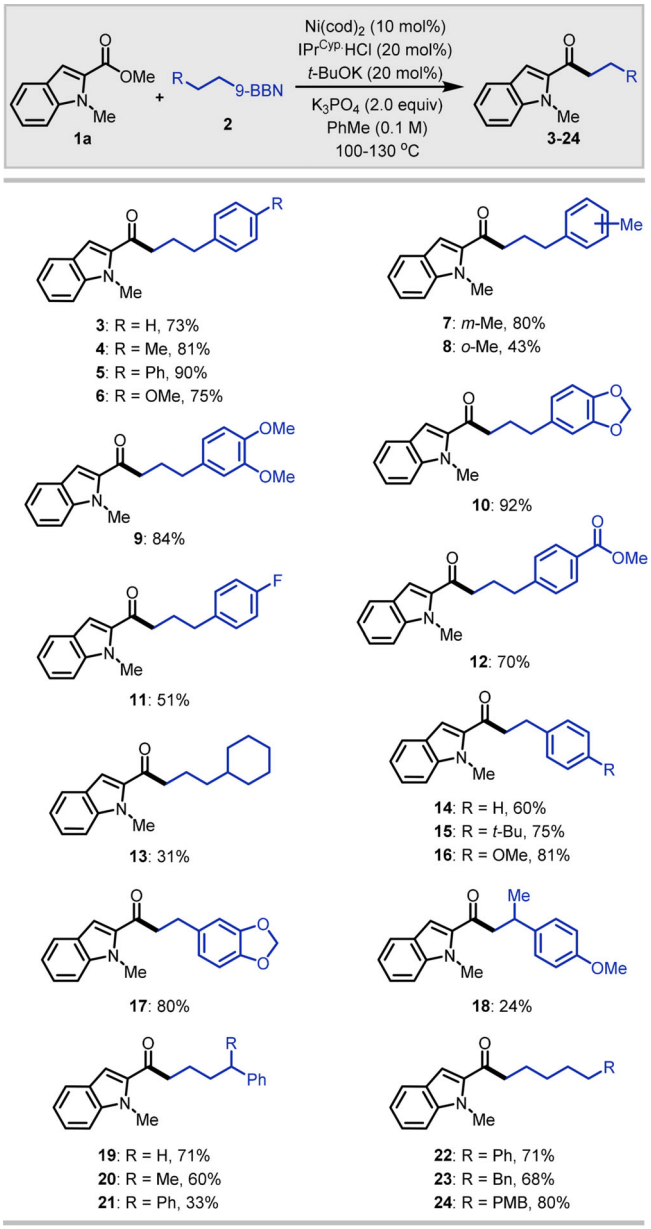
Entry	Deviation from standard conditions	Yield [%]
1	none	80
2	ligand = P^{n}Bu$_3$, P^{t}Bu$_3$ or PCy$_3$	0
3	ligand = dcype or dcypf	0
4	ligand = ICy·HBF$_4$	0
5	ligand = IPr·HCl	50
6	ligand = SIPr·HCl	45
7	ligand = IPr^{CHPh2}·HBF$_4$	58
8	ligand = IPr^{CPh3}·HCl	54
9	ligand = IPr′·HCl	60
10	KF instead of K$_3$PO$_4$	58
11	K$_2$CO$_3$ instead of K$_3$PO$_4$	50
12	no K$_3$PO$_4$	51
13	Ethyl ester instead of methyl ester	62
14	*t*-Butyl ester instead of methyl ester	30
15	Ni(cod)(dq) instead of Ni(cod)$_2$	44
16	Ni(OTf)$_2$ + Zn (2.0 equiv)	26
17	Reaction at 100 °C for 1 h	77



[a] Reactions run at 0.1 M concentration on 0.2 mmol scale. Yields determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

Results and Discussion

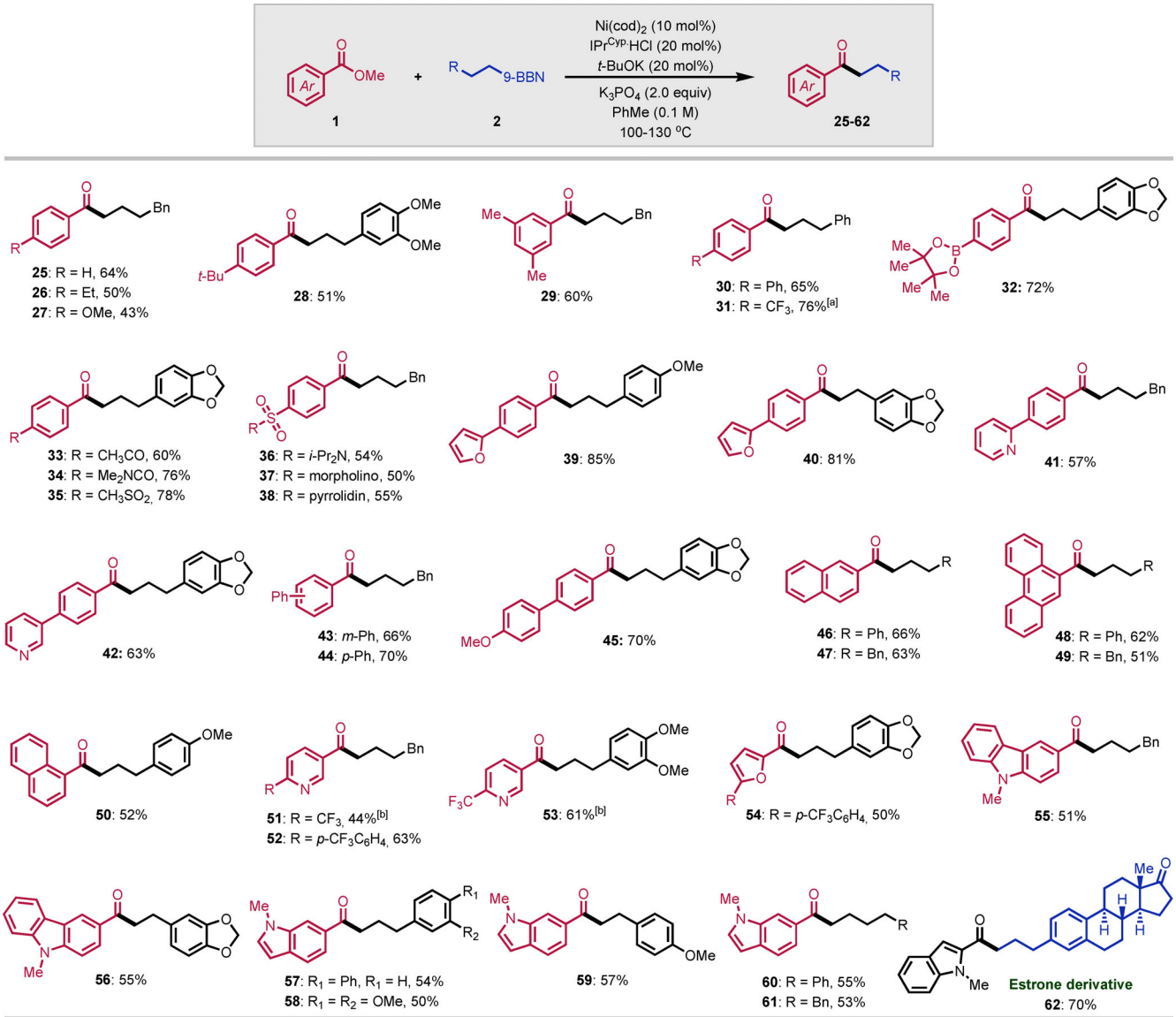
The coupling of methyl 1-methyl-1*H*-indole-2-carboxylate (**1a**) and B-alkyl-9-BBN[21] reactant **2a** was chosen as a model reaction. Using a Ni catalyst, K_3PO_4 as base, and toluene as solvent, the corresponding Suzuki–Miyaura ketone product **3** could be obtained in 80% yield (Table 1 entry 1). The use of



Scheme 2. Reaction scope of alkylborane reagents. General reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), Ni(cod)$_2$ (10 mol%), IPr^{Cyp}·HCl (20 mol%), *t*-BuOK (20 mol%), K$_3$PO$_4$ (0.4 mmol), toluene (0.1 M), 100–130 °C, 1–16 h (for specific conditions for each substrate, see the Supporting Information). Isolated yields are reported. Bn: benzyl, PMB: *p*-methoxybenzyl.

the 2,4,6-tricyclopentylaniline-derived *N*-heterocyclic carbine, which we refer to as IPr^{Cyp}, was found to be particularly important.[22] Monodentate (entry 2) and bidentate (entry 3) phosphines as well as the NHC ligand ICy (entry 4) gave no detectable product. While IPr^{Cyp} is analogous to the more common ligands IPr and SIPr, these gave consistently lower yields (entries 5 and 6). Remote steric bulk on ligands has previously been shown to result in improved activity in both Pd[23] and Ni-catalyzed[24] couplings. With this in mind, analogues IPr^{CHPh2}, IPr^{CPh3} and IPr′[25] were also investigated, providing moderate yields of 58%, 54%, and 60%, respectively (entries 7–9).

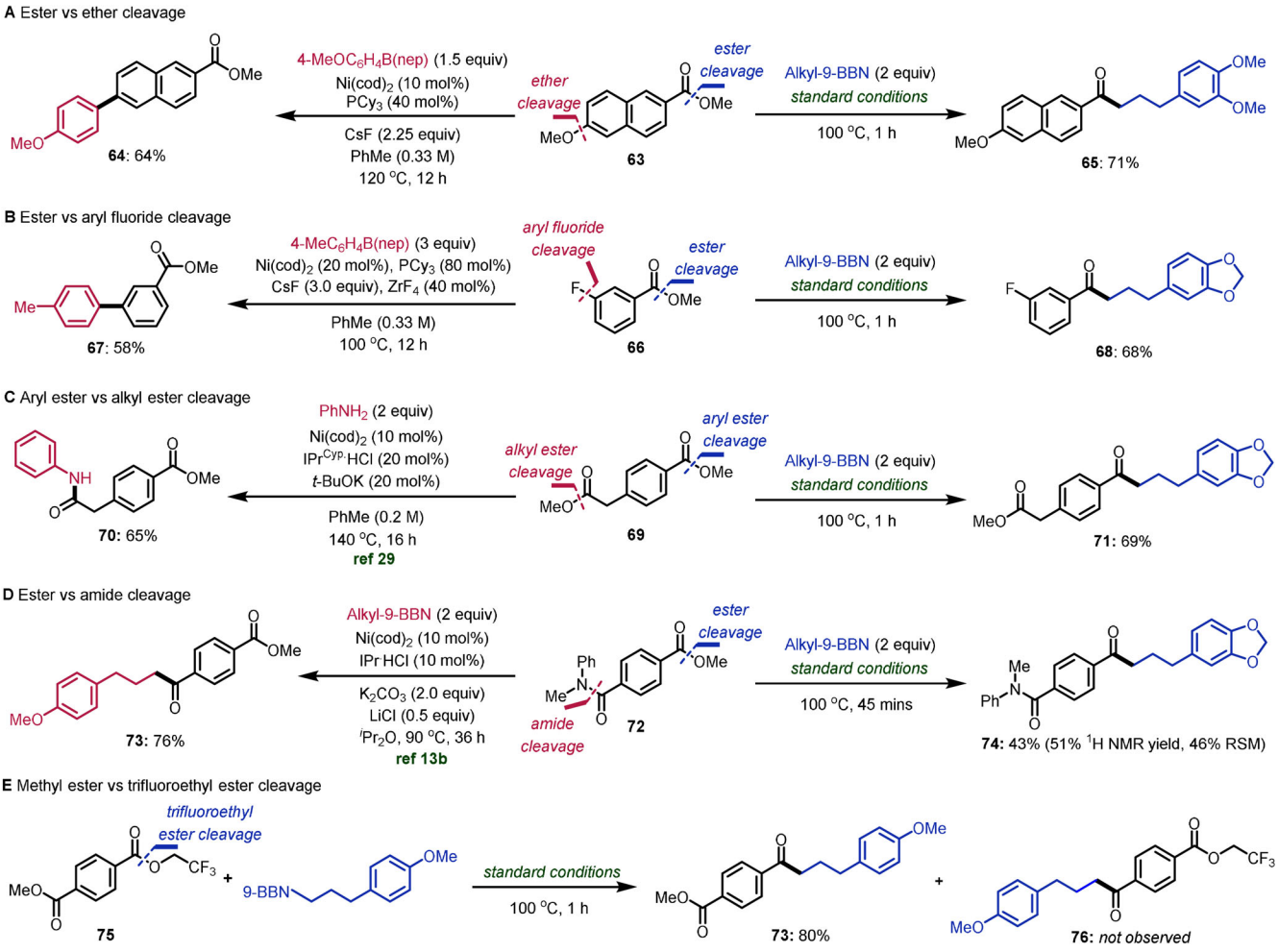
The choice of base was also important for obtaining high yields, with KF, K_2CO_3, and running in the absence of additional base[26] (beyond the *t*-BuOK required to deprotonate the ligand) all providing yields from 50–58% (entries 10–12). The reaction was not limited to use of methyl esters; both ethyl (entry 13) and *t*-butyl (entry 14) ester starting materials led to ketone **3**, albeit with reduced yield dependent on the steric bulk. Towards exploring air stable catalysts to enable the reaction to be setup outside a glovebox, Ni(cod)(dq)[27] (entry 15) and $Ni(OTf)_2$/Zn (entry 16) gave 44% and 26% yield, respectively. Lastly, when exploring the minimum needed temperature and time required, we observed high yields at 100 °C for 1 h (entry 17). Notably, in all experiments from Table 1, recovered **1a** was found to represent the majority of the remaining mass balance. Further, the use of alkylborane nucleophiles was found to be necessary. Extensive studies with arylboronic acids have thus far been unsuccessful. Further details on the reaction optimization can be found in the Supporting Information Tables S1–S6.



Scheme 3. Reaction scope of methyl esters and alkylboranes. General reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Ni(cod)_2$ (10 mol%), IPr^{Cyp}·HCl (20 mol%), *t*-BuOK (20 mol%), K_3PO_4 (0.4 mmol), toluene (0.1 M), 100–130 °C, 1–16 h (for specific conditions for each substrate, see the Supporting Information), isolated yields are reported. [a] KF (0.3 mmol) and KI (0.2 mmol) were used instead of K_3PO_4. [b] Ethyl ester was used instead of methyl ester.

With the optimized conditions in hand, we next evaluated the reaction scope of various alkylborane nucleophiles with temperatures from 100–130 °C and reaction times from 1–16 h, depending on the substrate (Scheme 2). The model ketone product **3** could be obtained in 73 % yield after purification. Functionalization of the *para* position of the alkylborane with Me, Ph and OMe substituents (**4**–**6**) all provided excellent yields (75–90 %). A *meta* methyl substituent gave **7** in 80 % yield, and an *ortho* methyl group gave ketone **8** in 43 % yields. With more electron rich arenes on the organoboron nucleophile, **9** and **10** were isolated in 84 % and 92 % yield. In contrast, electron withdrawing fluorine (**11**) and ester (**12**) groups on the *para* position gave slightly lower yields of 51 % and 70 %, respectively. Removing the aromatic ring completely led to a significant drop in yield, as evidenced by the 31 % yield of ketone **13**, derived from a cyclohexane-containing alkylborane nucleophile. Simple styrene derivatives also worked smoothly to give ketones **14**–**17** in good to excellent yields (60–81 %), though a more sterically hindered β-methyl alkylborane gave **18** in 24 % yield. Longer linear chains on the nucleophiles were also tolerated, providing **19**–**24** in yields ranging from 33–80 %. While most yields obtained during the scope evaluation were good, it is worth noting that seemingly minor changes to positions remote from the reactive C–B bond often resulted in surprisingly large changes in the yield.

We next explored the diversity of methyl ester electrophiles that could participate in the coupling (Scheme 3). First, simple methyl benzoate derivatives were tested, giving moderate to good yields of coupling products **25**–**31**. A boronic ester was also tolerated, giving ketone product **32** in 72 % yield and demonstrating chemoselectivity for the C-(sp^3)–B bond. An electrophilic acetyl group, (**33**) an *N*, *N*-dialkyl amide (**34**) and an electron-withdrawing methylsulfone substituent (**35**) were all tolerated. Derivatives of the sulfonamide-containing hyperuricemia drug probenecid were prepared in 50–55 % yield (**36**–**38**). Methyl benzoate derivatives bearing remote furan and pyridine groups participated in coupling to give ketones **39**–**42** in up to 85 % yield. Various esters bearing polycyclic aromatic backbones also gave the corresponding ketone products (**43**–**50**) in yields ranging from 51–70 %. Lastly, we evaluated a variety of heteroaromatic methyl esters. While unsubstituted methyl nicotinates could not be directly used, 2,5-disubstituted pyridines **51**–**53** could be formed in 44–63 % yield. Methyl esters directly attached to furan (**54**), carbazole (**55** and **56**), and the 6-position of indole (**57**–**61**) formed ketones with similar modest efficiency. Finally, an estrone-derived nucleophile could be used to form



Scheme 4. Orthogonal reactivity studies.

indole-bearing ketone **62** in 70% yield. Unfortunately, alkyl-substituted methyl esters could not be successfully alkylated with our conditions (See Figure S1, Supporting Information).

Methyl esters are generally considered to be inert functional groups for cross-coupling, particularly when compared to aryl chlorides, bromides, and iodides. Indeed, we found that these reactive carbon-halogen bonds were not tolerated in our scope. However, recent efforts have shown that many other strong bonds can participate in coupling chemistry with careful selection of the catalyst and nucleophile.[28] Towards understanding the chemoselectivity, several bifunctional substrates were tested under differing reaction conditions (Scheme 4). For example, the C(sp^2)–O bond of anisoles can be engaged in Suzuki–Miyaura coupling with a Ni/PCy_3 catalyst system and organoboronic ester nucleophile.[28a] When methyl ether-containing ester **63** was subjected to these conditions, a 64% yield of the C(sp^2)–O bond cleavage product was observed with no evidence of ester cleavage (Scheme 4a). Use of our standard conditions from Scheme 3 resulted in a complete switch in chemoselectivity, yielding ketone **65** in 71% yield with no evidence of ether cleavage. Similar results were observed with aryl fluoride-bearing ester **66** (Scheme 4b). Established conditions for Suzuki–Miyaura coupling via C-F bond cleavage[28b] yielded biaryl **67** in 58% yield. In contrast, our ester coupling conditions resulted in selective cleavage of the ester, providing **68** in 68% yield. To probe selectivity in the reaction of diesters, **69** was prepared. In our previous work on the reaction of esters with amine nucleophiles, this substrate underwent chemoselective cleavage at the α-alkyl ester group, giving amide **70** in 65% yield (Scheme 4c).[29] In contrast, the present conditions for alkylation showed complete selectivity for the α-aryl ester, providing ketone **71** in 69% yield. Next, we wanted to investigate the relative reactivity of amides and esters. *N*-Ph amides have been shown to be sufficiently activated to participate in Ni-catalyzed cross-coupling.[11a] Indeed, ester-bearing amide **72** has been already shown to undergo selective C–N bond cleavage by Rueping and co-workers, forming ketone **73** and leaving the ester untouched (Scheme 4d).[13b] Surprisingly, using our conditions with $Ni(cod)_2$/IPr^{Cyp}, coupling of the methyl ester occurs to provide ketone **74** in 51% NMR yield with 46% recovery of starting material, indicating that orthogonal reactivity between amides and esters is possible. Lastly, we probed if multiple esters could be differentiated based on electronics. With trifluoroethyl 4-methoxycarbonylbenzoate **75** selective cleavage of the trifluoroethanol-derived ester group was observed, affording **73** in 80% yields with no evidence of methyl ester cleavage.

Previous mechanistic studies on the Ni-catalyzed reaction of methyl esters with amine nucleophiles have suggested that a Ni^0/Ni^{II} cross-coupling mechanism is operative, with the Ni^0 oxidatively inserting into the ester C(acyl)–O bond.[15,30] This step was calculated to be endothermic and reversible, though with a reasonable kinetic barrier for the reaction temperatures used. Development of the Suzuki–Miyaura reaction described herein required extensive optimization and devia-

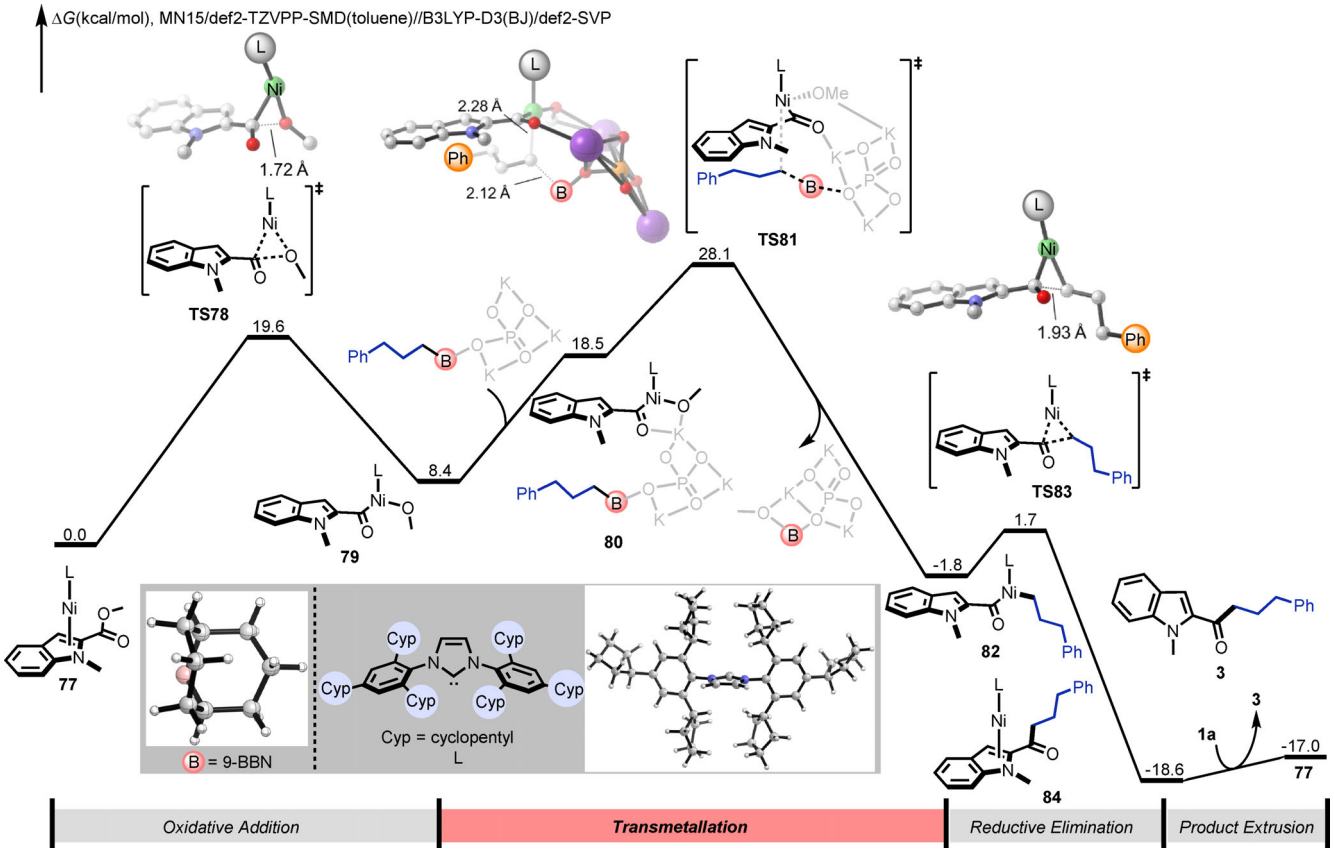


Figure 1. DFT-computed free energy profile of the most favorable pathway for the nickel-catalyzed Suzuki–Miyaura coupling of methyl esters.

tion from conditions originally developed for amide bond formation from methyl esters, suggesting challenges in the reaction beyond oxidative addition. DFT studies were thus carried out to better understand the similarities and differences from this previous work.

The DFT-computed free energy profile of the operative pathway of the Ni-catalyzed Suzuki–Miyaura coupling of methyl ester is provided in Figure 1, using methyl 1-methyl-1*H*-indole-2-carboxylate (**1a**) and B-alkyl-9-BBN (**2a**) as model compounds. From the substrate-coordinated nickel(0) complex **77**, oxidative addition via **TS78** cleaves the acyl C–O bond, leading to the acylnickel(II) intermediate **79**. The intrinsic barrier of acyl C–O bond activation via **TS78** is fairly low, which requires 19.6 kcal mol^{-1} from the oxidative addition pre-intermediate **77**. This is consistent with previous mechanistic studies.[14a,30] It should be noted that the bulky IPr^{Cyp} ligand prevents the formation of the off-cycle resting state Ni(NHC)$_2$.[15] Ni(IPr^{Cyp})$_2$ cannot be located in our computations despite extensive efforts. This destabilization of the Ni(NHC)$_2$ state by the bulky IPr^{Cyp} ligand also contributes to the ligand's high reactivity in the C–O bond activation. After the oxidative addition, **79** undergoes the transmetallation with the organoboron-K_3PO_4 complex[31] through **TS81** to generate the Ni^{II}(acyl)(alkyl) intermediate **82**. Subsequent acyl-alkyl reductive elimination occurs via **TS83**, producing the product-coordinated complex **84.** **84** eventually liberates the alkylated product **3** and regenerates species **77** for the next catalytic cycle. The DFT-computed free energy profile suggested that the on-cycle resting state is the product-coordinated nickel(0) complex **84**. The rate-limiting step is the transmetallation via **TS81**. The overall computed barrier of the catalytic cycle is 29.7 kcal mol^{-1} from the resting state **84** to the transmetallation transition state **TS81**.

Based on the above mechanistic understandings, we next explored the origins of the substituent effect on the reactivity of alkylboranes. In particular, we were curious about the non-intuitive roles of the remote cyclopentyl ring on the ligand and the remote aromatic ring on the organoboron nucleophile (e.g. **3** vs. **13**, Figure 2a). In transition state **TS81**, representing the rate-determining transmetallation towards ketone **3**, there exists a C–H···π interaction between the cyclopentyl group of the IPr^{Cyp} ligand and the phenyl substituent of the organoboron nucleophile. The C–H···π distance is 2.6 Å, and this favorable interaction was further confirmed by IGM analysis (Figure 2b). Upon changing to a saturated organoboron nucleophile bearing a cyclohexyl group, the favorable C–H···π interaction no longer exists. The cyclopentyl group from the IPr^{Cyp} ligand and the cyclohexyl ring on the organoboron are sterically repulsive to each other in **TS85**. This increases the overall transmetallation barrier to 29.5 kcal mol^{-1},[32] which is consistent with the significant drop in reactivity when forming ketone **13**. These mechanistic understandings highlight the synergistic design of ligand and substrate in promoting the desired Ni-catalyzed cross-coupling reactions.

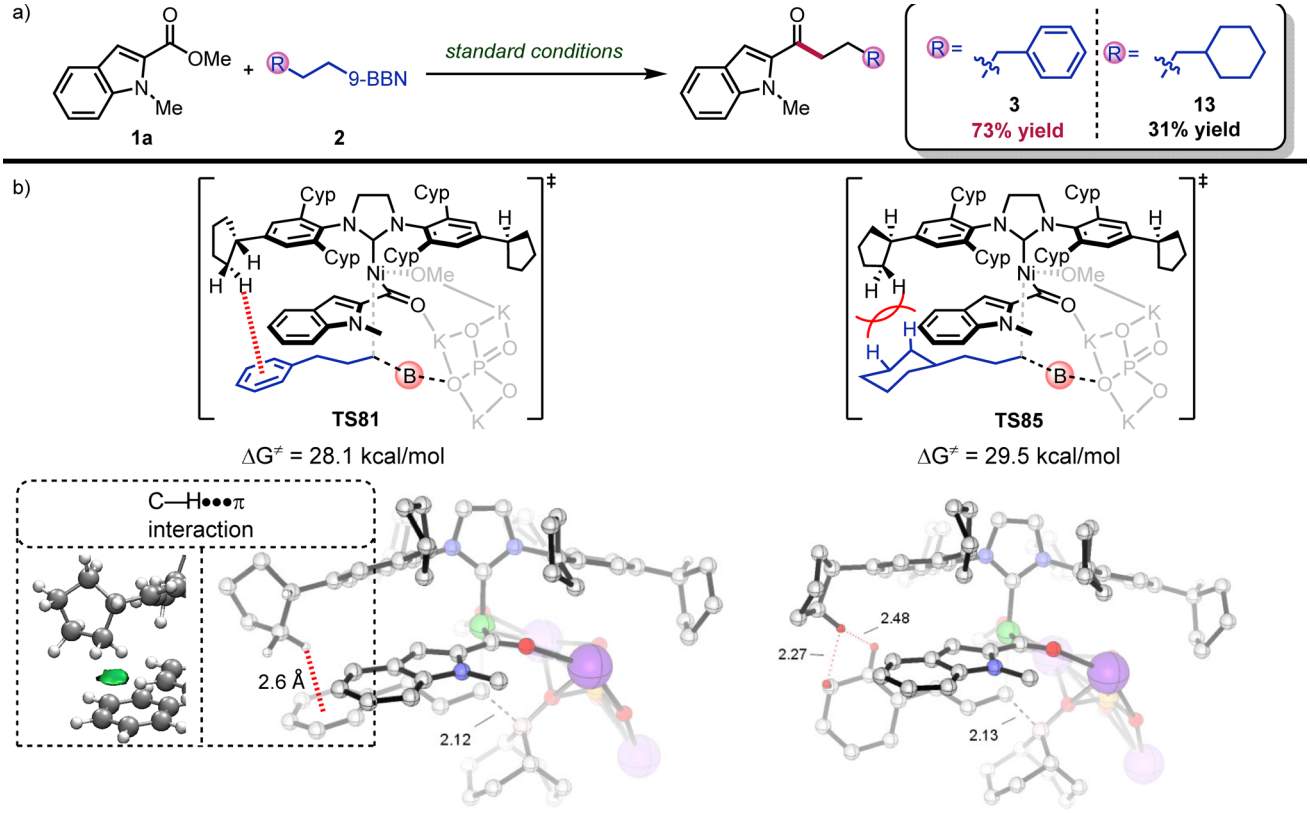


Figure 2. Optimized transition-state structures and free energy barriers of transmetallation with phenyl- and cyclohexyl-substituted organoboron nucleophile. Free energy barriers are compared to the substrate-coordinated complex **77**. Irrelevant hydrogens are omitted in the structure diagrams.

Conclusion

The direct synthesis of ketones by the reaction of abundant methyl esters and organometallic nucleophiles is a long-standing challenge. By employing a Ni^0 catalyst capable of oxidatively adding into the strong C(acyl)–O bond of these substrates, an organoboron reagent can react by transmetallation via a Suzuki–Miyaura-type reaction mechanism. Since these nucleophiles are inert towards ketones, no secondary addition products are observed as is the case when more aggressive organometallic reagents are used. The seldom used ligand IPr^{Cyp}, derived from 2,4,6-tricyclopentyl aniline, is found to be particularly important for obtaining high yields. DFT studies suggest the Ni-NHC catalyst formed in situ undergoes relatively facile oxidative addition into the ester C(acyl)–O bond, with transmetallation being rate-limiting. The reaction was observed to be particularly sensitive to remote substituents, which can be explained by presence of stabilizing non-covalent interactions between the NHC ligand and the substrate in the transmetallation step. Finally, the ester cross-coupling reaction displays remarkable orthogonality to other Ni-catalyzed strong-bond activation methods capable of coupling aryl ethers, aryl fluorides, and amides. Further studies are underway using the information discussed herein to expand the scope of this reaction beyond aryl-substituted esters and alkylboron nucleophiles.

Acknowledgements

Financial support for this work was provided by BASF, the National Science and Engineering Research Council of Canada (NSERC), the Canada Research Chair program, the National Natural Science Foundation of China (21702182 and 21873081, X.H.), Fundamental Research Funds for the Central Universities (2020XZZX002-02, X.H.), and the State Key Laboratory of Clean Energy Utilization (ZJUCEU2020007, X.H.). Calculations were performed on the high-performance computing system at the department of chemistry, Zhejiang University. Martin McLaughlin, Mathias Schelwies, Stephan Zuend, and Roland Götz (BASF) are thanked for helpful discussions. The Canadian Foundation for Innovation (CFI) and the Ontario Ministry of Research, Innovation, & Science are thanked for essential infrastructure. We thank Jacob Jessiman (Newman lab) for the synthesis of some starting materials.

Conflict of interest

The authors declare no conflict of interest.

Keywords: cross-coupling · esters · ketones · nickel · Suzuki–Miyaura reactions

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[32] The full free energy profile towards forming **13** is provided in the Supporting Information.

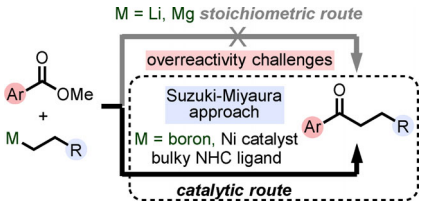
Manuscript received: March 7, 2021
Accepted manuscript online: April 1, 2021
Version of record online: ■■ ■■, ■■■■

Research Articles

Nickel Catalysis

Y.-L. Zheng, P.-P. Xie, O. Daneshfar, K. N. Houk,* X. Hong,* S. G. Newman* _____ ▮▮▮▮–▮▮▮▮

Direct Synthesis of Ketones from Methyl Esters by Nickel-Catalyzed Suzuki–Miyaura Coupling



Methyl esters are shown to participate in intermolecular Suzuki–Miyaura cross-coupling reactions. Due to the mild nature of organoboron reagents, the product ketones are inert to the reaction conditions, avoiding over reactivity issues prominent with more aggressive organometallic nucleophiles.