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Mechanism-Based Design of an Amide-Directed Ni-Catalyzed Arylboration of Cyclopentene Derivatives

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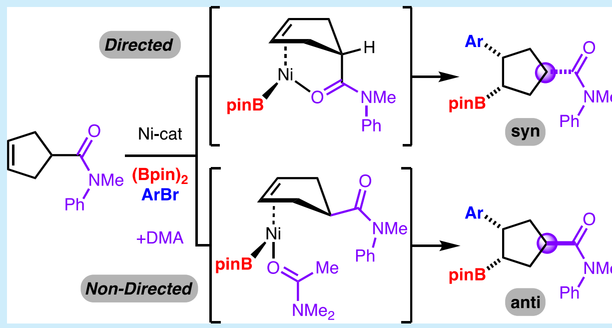
ABSTRACT: A method for amide-directed Ni-catalyzed diastereoselective arylboration of cyclopentenes is disclosed. The reaction allows for the synthesis of sterically congested cyclopentane scaffolds that contain an easily derivatized boronic ester and amide functional handles. The nature of the amide directing group and its influence on the reaction outcome are investigated and ultimately reflect a predictably selective reaction based on the solvent and base counterion.



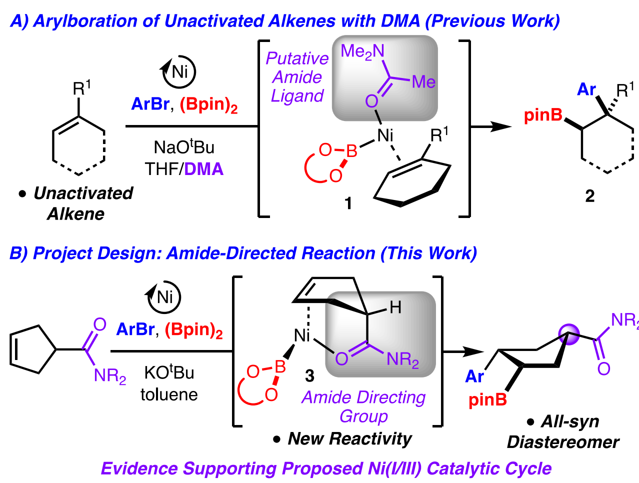
Conjunctive cross-coupling is a powerful method for chemical synthesis because multiple bonds are formed in a single operation, resulting in the rapid generation of molecular complexity.[1] In particular, carboboration is an important variant of conjunctive cross-coupling due to the simultaneous generation of a C−C bond and a highly versatile C−B bond in a single transformation.[2] Through Pd/Cu,[3] Ni/Cu,[4] Cu,[5] Ni,[6] and Pd catalysis,[7] our group and others have developed arylboration reactions of alkenes activated through either conjugation or strain. However, until recently, reports on the arylboration of unactivated alkenes have remained absent in the literature.[8]

To address the challenge of functionalizing unactivated alkenes, our lab developed a Ni-catalyzed arylboration reaction capable of engaging a wide range of these substrates (Scheme 1A).[9,10] Key to the development of this method was the inclusion of *N*,*N*-dimethylacetamide (DMA) as a cosolvent to suppress the formation of byproducts resulting from the β-hydride elimination of alkyl−[Ni] complexes.[10] These reactions likely proceed through a *syn* boryl nickelation of the alkene, forming an alkyl−[Ni] complex that can undergo reaction with an aryl bromide.

Over the course of the previous study, the results of a mechanistic investigation suggested that DMA was coordinated to Ni during migratory insertion.[10] We then reasoned that an amide group with appropriate proximity to the alkene (**3**) could direct arylboration to deliver all-*syn* products that would be inaccessible by other methods (Scheme 1B). This advance would be significant, as it would allow for the stereocontrolled synthesis of versatile all-*syn* products.

Directing groups have previously been employed in a variety of systems for alkene difunctionalization reactions in order to control the regioselectivity of a migratory insertion event and to

Scheme 1. Arylborations of Unactivated Alkenes



prevent β-hydride elimination pathways from alkyl−metal intermediates.[11−19] For Ni-catalyzed difunctionalization reactions, directing groups including acetate,[11] imines,[12] aminoquinone,[8,13] aminopyrimidine,[14] N-heterocycles,[15] amides,[16] and carboxylic acids have been disclosed.[17] Notably, a recent report by Engle describes the use of 8-aminoquinoline to achieve regioselective, and in one case diastereoselective, Pd-catalyzed

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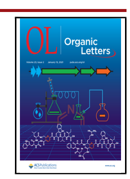

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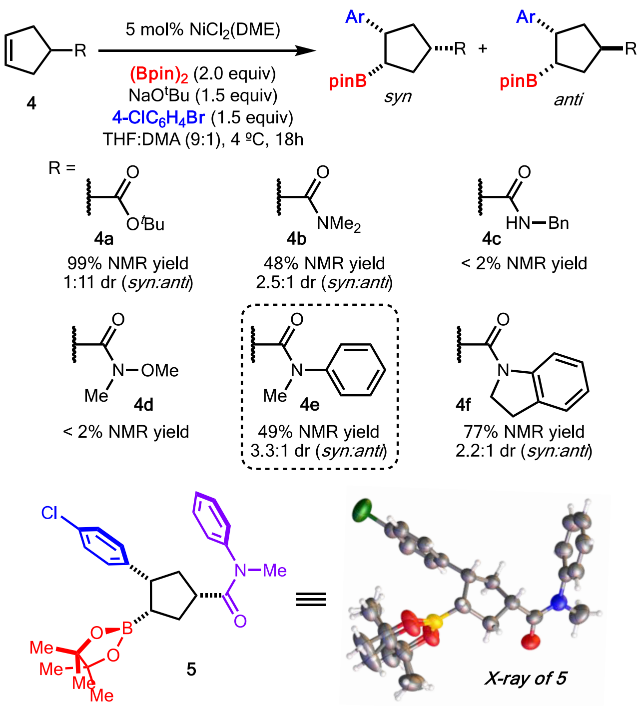
arylboration.[18] In this reaction, the Pd catalyst coordinates with the directing group, controlling the regioselectivity of the migratory insertion via formation of a five-membered palladacycle.

Our strategy is based on a similar premise in that an amide placed proximal to the alkene can be used to direct the migratory insertion event. Preliminary investigation using previously reported conditions[10] revealed that the use of dimethylamide **4b** allowed for formation of the *syn* diastereomer, thus confirming the viability of our approach (Scheme 2). Evaluation

Scheme 2. Evaluation of Directing Groups[a]

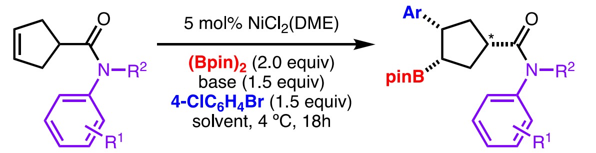


[a]Yield refers to the yield of both diastereomers as determined by ^{1}H NMR analysis of the unpurified mixture with an internal standard.

of amides revealed that use of *N*-methyl-*N*-phenyl derivative **4e** led to an increase in diastereoselectivity favoring diastereomer **5**, as confirmed by X-ray crystallography. It is important to note that the reaction of **4a** resulted in the formation of the *anti* diastereomer, presumably through a nondirected sterically guided pathway.

After the feasibility of the directed arylboration was established, the reaction conditions were optimized to favor binding of the pendent amide to Ni. Since DMA can compete with the pendent amide for coordination with Ni, it was omitted from the reaction, resulting in an increase in diastereoselectivity but a concomitant decrease in yield (Scheme 3, entry 3). Improving the yield without loss of diastereoselectivity proved to be a delicate balance of variables in the reaction conditions. The yield of the reaction could be restored through the use of toluene as the solvent instead of THF; however, the diastereoselectivity was lowered. The yield was significantly improved by the use of increased equivalents of reagents at a higher temperature (Scheme 3, entry 6). Furthermore, in an attempt to improve the diastereoselectivity of the reaction, electronically (Scheme 3, entries 7 and 8) and sterically (Scheme 3, entries 9 and 10) modified directing groups were explored, but no added benefit was found. Lastly, switching the counterion of

Scheme 3. Optimization of the Reaction Conditions[a]



entry	solvent	R^1	R^2	base	yield[a]	dr (syn:anti)[b]
1	THF:DMA (9:1)	-H	-Me	NaO^{t}Bu	49%	3.3:1
2	DMA	-H	-Me	NaO^{t}Bu	60%	1:1.4
3	THF	-H	-Me	NaO^{t}Bu	41%	20:1
4	2-MeTHF	-H	-Me	NaO^{t}Bu	37%	18:1
5	toluene	-H	-Me	NaO^{t}Bu	71%	10:1
6[c]	toluene	-H	-Me	NaO^{t}Bu	86%	12:1
7[c]	toluene	-3-Cl	-Me	NaO^{t}Bu	57%	7:1
8[c]	toluene	-4-OMe	-Me	NaO^{t}Bu	70%	11:1
9[c]	toluene	-2-Me	-Me	NaO^{t}Bu	76%	10:1
10[c]	toluene	-H	-Et	NaO^{t}Bu	68%	20:1
11[c]	toluene	-H	-Me	KO^{t}Bu	83%	23:1

[a]Yield refers to the yield of both diastereomers as determined by ^{1}H NMR analysis of the unpurified mixture with an internal standard. [b]Diastereomeric ratio at the indicated carbon. [c]The reaction was run with 10% $NiCl_2$(DME), $(Bpin)_2$ (4.0 equiv), base (3.0 equiv), and 4-ClC_6H_4Br (2.0 equiv) at 50 °C.

the base from Na^+ to K^+ increased the diastereoselectivity significantly without a substantial loss of yield, culminating in an optimal set of conditions (Scheme 3, entry 11).

Next, the scope of the directed arylboration was investigated. With respect to the alkene component, the standard substrate (product **5**) reacted smoothly (Scheme 4). Substituents at the α-position of the amide were tolerated (product **6**), albeit with lower diastereoselectivity due to allylic strain with the amide. When the α-substituent was constrained to a ring within the amide, this strain was eliminated, and the high diastereoselectivity was restored (product **7**). Additionally, trisubstituted alkenes were tolerated and allowed for the formation of quaternary carbons (products **8** and **9**). Notably, these examples represent the formation of densely substituted cyclopentanes. At this point, the alkene scope is limited to cyclopentene derivatives; cyclohexene-derived substrate **16** was not reactive, but this is consistent with previous reports demonstrating that cyclohexene is significantly less reactive than cyclopentene.[9,10] The reaction was also tolerant of a variety of aryl bromides, including electron-deficient (product **5**), electron-rich (product **11**), and sterically demanding (products **12** and **14**) examples. Additionally, the functional group tolerance was evaluated and included tertiary amine and aniline derivatives (products **15** and **18**, respectively). Heteroaryl bromides such as pyridine (product **19**), indole (product **17**), and furan (product **20**) also functioned well in the reaction. Alkenylboration was also achieved through the use of a vinyl bromide (product **21**), installing two easily derivatized functional groups in a single transformation.

Furthermore, the reaction was performed on a gram scale and worked with similar yield and selectivity as for the smaller-scale reactions (Scheme 5A). To demonstrate the synthetic utility of the products, the boronic ester and amide units of **5** were functionalized through oxidation (**22**), homologation (**24**), olefination (**26**), hydrolysis (**23**), and reduction (**25**) (Scheme 5B). Confirmation of the stereochemistry of **23** by X-ray crystallography verified that epimerization of the α-stereogenic

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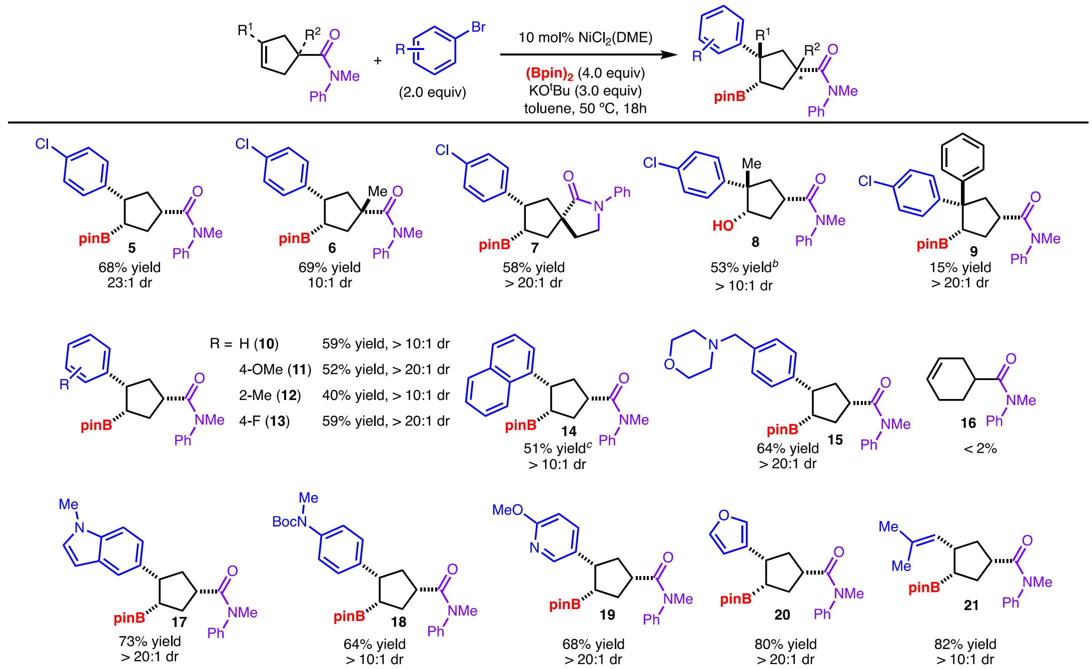
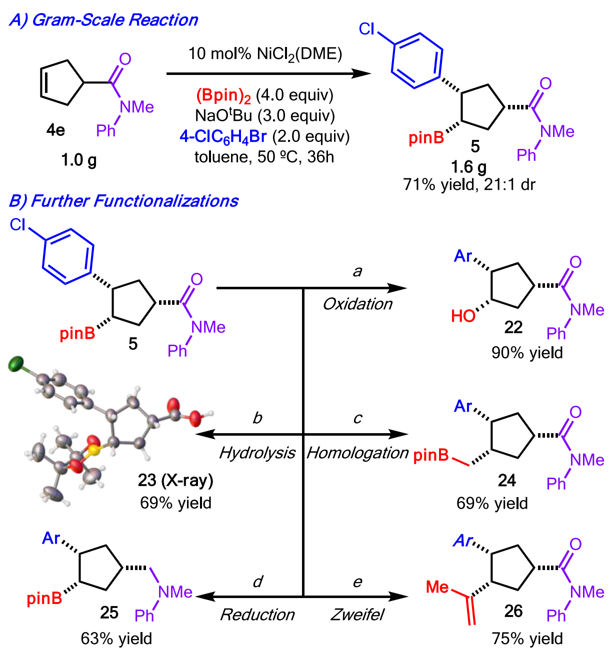
Scheme 4. Reaction with Various Alkenes and Aryl Bromides[a]



[a]Yield refers to the isolated yield of the *syn* diastereomer product after silica gel column chromatography and is reported as the average of two or more experiments (0.5 mmol scale). [b]Isolated as a single diastereomer after oxidation to the alcohol; see the Supporting Information for details. [c]Reaction time = 40 h.

Scheme 5. Gram-Scale Reaction and Further Functionalizations[a]



[a]Yield refers to the isolated yield of the product after silica gel column chromatography. Reagents and conditions in (B): (*a*) H_2O_2 (3.0 equiv), NaOH (10 equiv), THF, 0 °C to rt, 10 h. (*b*) (i) 6 N HCl in H_2O, 100 °C, 15 h; (ii) pinacol (2.0 equiv), toluene, rt, 3 h. (*c*) ^{n}BuLi (2.2 equiv), CH_2Br_2 (2.5 equiv), THF, −78 °C to rt, 18 h. (*d*) DIBAL-H (4.0 equiv), THF, 0 °C to rt, 2 h. (*e*) (i) ^{t}BuLi (8.0 equiv), 2-bromopropene (4.0 equiv), THF, −78 °C, 3h; (ii) I_2 (4.0 equiv), MeOH, 1.5 h.

center did not take place during hydrolysis. Through these transformations, a diverse range of cyclopentane derivatives can be prepared with control of stereochemistry.

The impact of the directing group on the resultant stereochemistry is intriguing and warranted further mechanistic investigation. Significant changes in diastereoselectivity were observed when the counterion of the base was modified (Scheme 6A). More oxophilic counterions, such as Li^+, can compete with Ni to chelate with the amide directing group, resulting in significantly diminished diastereoselectivity. When the corresponding crown ether was added to the reaction mixture to sequester the counterion, an increase in diastereoselectivity was observed in all cases. To simplify the reaction conditions, crown ethers were not used in the optimum conditions but could be added as a supplement to improve the diastereoselectivity. A trend ultimately favoring the *anti* diastereomer was observed as the amount of DMA was increased.[10] This is likely due to disrupted binding of the substrate-bound amide to Ni by DMA to induce a sterically guided reaction, resulting in the formation of *anti* diastereomer **27** (Scheme 6B). Finally, using DMA as the solvent in the presence of oxophilic counterions such as Na^+ or Li^+ increases the selectivity for the *anti* diastereomer by competitive binding with the directing group. Altogether, the mechanistic data provide further support for the Ni-catalyzed arylboration of alkenes and, in particular, the role of amide-based additives in controlling the stereochemical course of the reaction.

In summary, a Ni-catalyzed directed arylboration reaction has been developed. The method presents a strategy to deliver versatile and highly substituted cyclopentane products. The mechanistic investigation highlights the role of the amide component, either as a bound substrate or external competitive ligand, in controlling the stereodivergent outcomes of the reaction.

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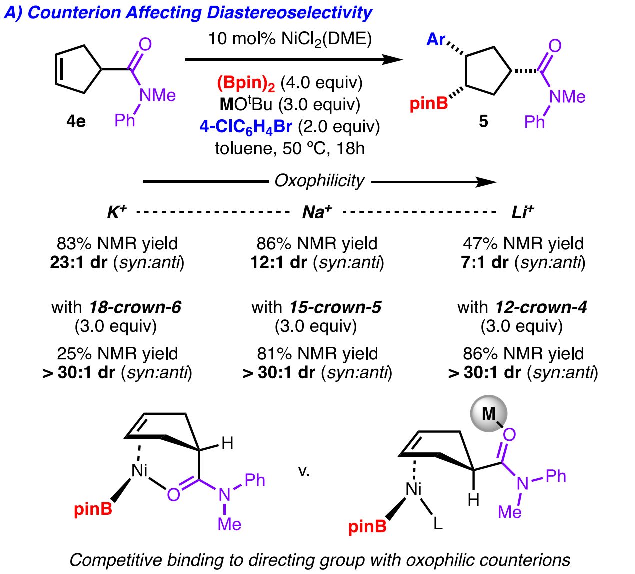
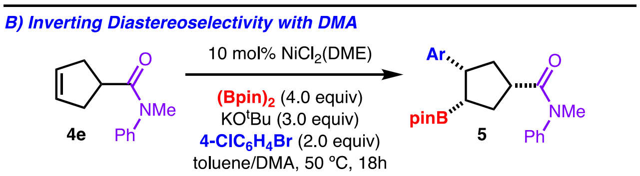
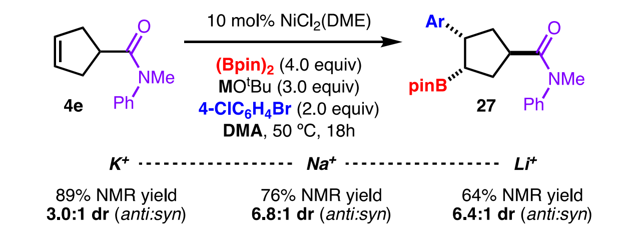
Scheme 6. Mechanistic Experiments





entry	toluene : DMA	syn (5) : anti (27)
1	100 : 0	23 : 1
2	90 : 10	26 : 1
3	80 : 20	16 : 1
4	67 : 33	6.1 : 1
5	50 : 50	2.2 : 1
6	33 : 67	1 : 1.3
7	20 : 80	1 : 1.6
8	10 : 90	1 : 2.4
9	0 : 100	1 : 3.0



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04208.

FAIR data, including the primary NMR FID files, for compounds **4b–f**, **5–27**, and **SI1–SI19** (ZIP)

Experimental procedures, characterization data, mechanistic studies, X-ray crystal structures, and NMR spectra (PDF)

Accession Codes

CCDC 2044395 and 2044396 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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