Organic LETTERS

Letter

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Alkene-Assisted Nickel-Catalyzed Regioselective 1,4-Addition of Organoboronic Acid to Dienones: A Direct Route to All-Carbon Quaternary Centers

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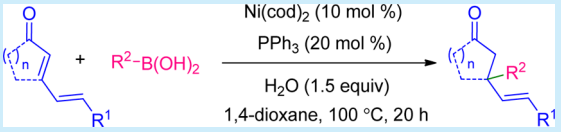
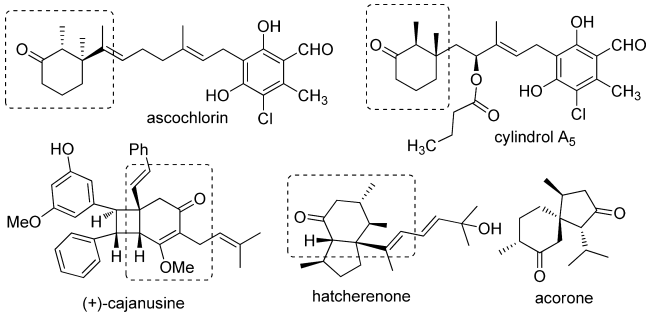
Supporting Information

ABSTRACT: A nickel-catalyzed highly regioselective 1,4-addition reaction of boronic acids to dienones to form products with an all-carbon quaternary center is described. The 3-alkenyl group of dienones is the key for the reaction to proceed smoothly. A mechanism involving the coordination of the dienyl group to the nickel center is proposed.



All-carbon quaternary centers are an important feature found in many natural and bioactive molecules.[1] In particular, cyclohexane rings bearing an all-carbon quaternary center are often found in natural products and are an important building block in organic synthesis (Scheme 1).[2] Formation of an all-carbon quaternary center is challenging synthetically due to the steric hindrance of the four carbon groups and the limited reliable methods available.[3]

Scheme 1. Natural Products Containing an All-Carbon Quaternary Center



Transition-metal-catalyzed conjugate addition of carbon nucleophiles (R−MX_n; where M is Mg, Al, Zr, Li, Zn, B, or Si) to α,β-unsaturated carbonyl compounds is considered a prevailing method for the construction of all-carbon quaternary centers.[1,4,5] However, controlling the regioselectivity of conjugate addition to a polyconjugated substrate is a challenging task due to the presence of several competitive electrophilic sites (1,2-, 1,4-, and 1,6-additions).[6] In addition, most of these reactions are effective only with highly air- and moisture-sensitive organometallic reagents such as organozinc, organoaluminum, organomagnesium, and organozirconium compounds. The less reactive boron and silyl reagents worked well only with catalysts containing noble metals such as Rh and Pd.[1−6] Nickel complexes are also known to catalyze conjugate addition reactions to α,β-unsaturated alkenes, but none of them were reported for the addition to dienones and the formation of all-carbon quaternary centers.[7] As we have been interested in nickel-catalyzed organic transformations,[8] herein we report a nickel-catalyzed, highly regioselective 1,4-addition reaction of boronic acids to dienones to form products with an all-carbon quaternary center.

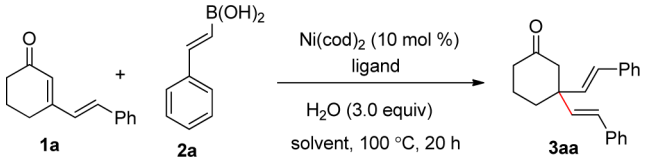
The reaction of 3-styrylcyclohex-2-enone (**1a**) with trans-styrylboronic acid (**2a**) in the presence of $Ni(cod)_2$ (10 mol %), PPh_3 (20 mol %) and H_2O (1.5 equiv) in 1,4-dioxane at 100 °C for 20 h gave 1,4-addition product **3aa** in 90% isolated yield (Table 1, entry 15). The product was thoroughly characterized by ^1H and ^{13}C NMR and HRMS data. The catalytic reaction depends greatly on the ligand, the amount of water, and solvent used, and the results are summarized in Table 1. Among the solvents tested, 1,4-dioxane appeared to afford the best yield (entries 3 and 15). MeOH and EtOAc also gave product **3aa** in 77 and 45% yields, respectively. The catalytic reaction proceeds less effectively in the absence of PPh_3 or with chelating ligands (entries 8−12). The reaction conducted in the absence of water gave only a trace of product (entry 13). No product **3aa** was observed in the absence of $Ni(cod)_2$ or using NiI_2 and $NiBr_2$ as the catalyst.

Next, to understand the scope of the present catalytic reaction, we tested the reactivity of various aryl and styrylboronic acids with **1a**. Thus, the reaction of **1a** with 4-Me and 4-OMe substituted styrylboronic acids under standard reaction conditions gave the respective products **3ab** and **3ac** in 98% and 66% yields, respectively (Table 2, entries 2−3). The reaction of phenylboronic acid (**2d**) with **1a** gave the desired product **3ad** in 91% yield. Similarly, different para substituted phenylboronic acids **2e−g** reacted smoothly with **1a** to form the respective products **3ae−ag** in excellent yields (entries 5−7). Treatment of 3-methoxyphenylboronic acid (**2h**) and *o*-

Received: March 20, 2014
Published: May 9, 2014

dx.doi.org/10.1021/ol500838h | *Org. Lett.* 2014, 16, 2806−2809

Table 1. Reaction Optimization[a]



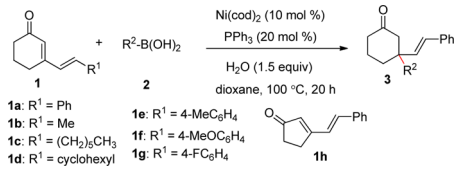
entry	ligand/mol %	H_2O/mmol	solvent	yield (%)[b]
1	PPh_3/20	0.90	MeOH	77
2	PPh_3/20	0.90	toluene	trace
3	PPh_3/20	0.90	1,4-dioxane	99
4	PPh_3/20	0.90	$ClCH_2CH_2Cl$	trace
5	PPh_3/20	0.90	CH_3CN	–
6	PPh_3/20	0.90	EtOAc	45
7	PPh_3/20	0.90	DMF	–
8	dppe/10	0.90	1,4-dioxane	29
9	dppp/10	0.90	1,4-dioxane	14
10	dppb/10	0.90	1,4-dioxane	53
11	*rac*-BINAP/10	0.90	1,4-dioxane	trace
12	–	0.90	1,4-dioxane	47
13	PPh_3/20	0	1,4-dioxane	trace[c]
14	PPh_3/20	0.90	1,4-dioxane	81[d]
15	PPh_3/20	0.450	1,4-dioxane	91(90)[e]
16	PPh_3/10	0.450	1,4-dioxane	73
17	PPh_3/10	0.450	1,4-dioxane	51[f]
18	PPh_3/10	0.450	1,4-dioxane	62[f,g]

[a]Unless otherwise mentioned, all reactions were carried out using **1a** (0.30 mmol), **2a** (0.90 mmol), and $Ni(cod)_2$ (0.030 mmol) in 1.2 mL of solvent at 100 °C for 20 h. [b]The yields were determined by ^1H NMR integration using mesitylene as an internal standard. [c]Reaction was conducted in dry 1,4-dioxane in the absence of H_2O. [d]Reaction was conducted at 80 °C. [e]Reaction was carried out using **2a** (0.450 mmol). [f]5 mol % $Ni(cod)_2$ was used. [g]Reaction was conducted for 36 h. Yield in the parentheses was isolated.

tolylboronic acid (**2i**) with **1a** under similar reaction conditions afforded conjugate addition products **3ah–i** in 72% and 80% isolated yields, respectively (entries 8–9). Highly substituted arylboronic acids **2j–k** also underwent the expected addition reaction with **1a** to afford products **3aj–k** in good yields (entries 10 and 11). A heterocyclicboronic acid such as thiophen-2-ylboronic acid (**2l**) was also compatible in the present catalytic reaction to form product **3al** in 62% yield. In addition to different boronic acids, we also examined the effect of different substitutions on the dienone moiety. Thus, the reaction of (3-propenyl)cyclohex-2-enone **1b** with **2a** and **2d** under the standard reaction conditions afforded products **3ba** and **3bd** in 47% and 50% yields, respectively. In a similar manner, bulkier alkyl substituted dienones **1c–d** reacted with **2a** to give the desired products in good yields (entries 14–15). In addition to alkyl substituted dienones, differently substituted styrylcyclohexenones **1e–g** also provide the desired products under standard reaction conditions (entries 16–18, 22–24). Furthermore, a cyclopentenone substrate (**1h**) reacted smoothly with **2a** to afford desired product **3ha** in 54% yield. Unfortunately, the reaction using alkylboronic acids did not proceed to give the expected products under similar reaction conditions.

The presence of a vinyl moiety at the 3-position of cyclohexenone is essential for the success of the present catalytic reaction. Cyclohexenones with a methyl-, phenyl-, and allyl-substitution at the 3-position (**1i–l**) did not react with styryl- or phenylboronic acid to form 1,4-addition products

Table 2. Scope of the Ni-Catalyzed Reaction[a]



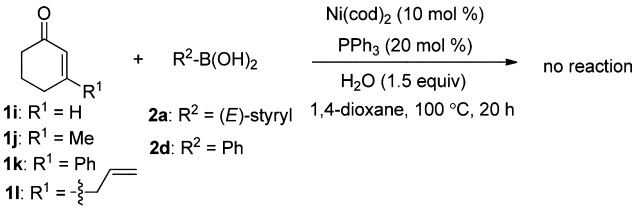
entry	1	2	3	yield (%)[b]
1	**1a**	**2a**	**3aa**: R = H	90
2	**1a**	**2b**	**3ab**: R = Me	98
3	**1a**	**2c**	**3ac**: R = OMe	66
4	**1a**	**2d**	**3ad**: R = H	91
5	**1a**	**2e**	**3ae**: R = 4-Me	81
6	**1a**	**2f**	**3af**: R = 4-OMe	79
7	**1a**	**2g**	**3ag**: R = 4-CF_3	81
8	**1a**	**2h**	**3ah**: R = 3-OMe	72
9	**1a**	**2i**	**3ai**: R = 2-Me	80
10	**1a**	**2j**	**3aj**: R = 3,5-Me	53
11	**1a**	**2k**	**3ak**: R = 3,5-F	96
12	**1a**	**2l**	**3al**	62
13	**1b**	**2a**	**3ba**: R^1 = Me	47
14	**1c**	**2a**	**3ca**: R^1 = $(CH_2)_5CH_3$	63
15	**1d**	**2a**	**3da**: R^1 = cyclohexyl	68
16	**1e**	**2a**	**3ea**: R^1 = 4-MeC_6H_4	82
17	**1f**	**2a**	**3fa**: R^1 = 4-$MeOC_6H_4$	96
18	**1g**	**2a**	**3ga**: R^1 = 4-FC_6H_4	68
19	**1b**	**2d**	**3bd**: R^1 = Me	50
20	**1c**	**2d**	**3cd**: R^1 = $(CH_2)_5CH_3$	80
21	**1d**	**2d**	**3dd**: R^1 = cyclohexyl	76
22	**1e**	**2d**	**3ed**: R^1 = 4-MeC_6H_4	76
23	**1f**	**2d**	**3fd**: R^1 = 4-$MeOC_6H_4$	97
24	**1g**	**2d**	**3gd**: R^1 = 4-FC_6H_4	61
25	**1h**	**2a**	**3ha**	54

[a]Unless otherwise mentioned, all reactions were carried out using **1** (0.30 mmol), **2** (0.45 mmol), $Ni(cod)_2$ (0.030 mmol), PPh_3 (0.060 mmol), and H_2O (0.45 mmol) in 1.2 mL of 1,4-dioxane at 100 °C for 20 h. [b]Isolated yield.

dx.doi.org/10.1021/ol500838h | *Org. Lett.* 2014, 16, 2806–2809

under similar reaction conditions (Scheme 2). Similarly, methyl vinyl ketone showed a trace of the expected 1,4-addition

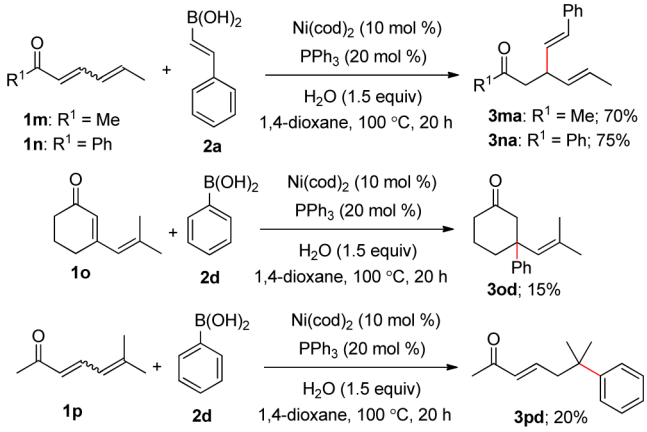
Scheme 2. Effect of Substitution on 3-Substituted Cyclohexenone



product in the crude NMR. The results suggested that the alkene moiety in substrate **1** is essential and probably acts as a chelating ligand to the nickel catalyst center.[9] In this context, we tried to stabilize Ni-complexes (Scheme 4, intermediates **I** and **II**) by addition of an external olefin (styrene or norbornene)[10] to the reaction of **1j** with **2d** shown in Scheme 2, but no expected 1,4-addition products were detected.

To understand the reaction scope further, we examined the reactivity of acyclic dienones under similar reaction conditions. Thus, the reaction of hepta-3,5-dien-2-one (**1m**) and 1-phenylhexa-2,4-dien-1-one (**1n**) with **2a** afforded the desired 1,4-addition products **3ma** and **3na** in 70% and 75% yields, respectively (Scheme 3). It is interesting to note that 6,6-

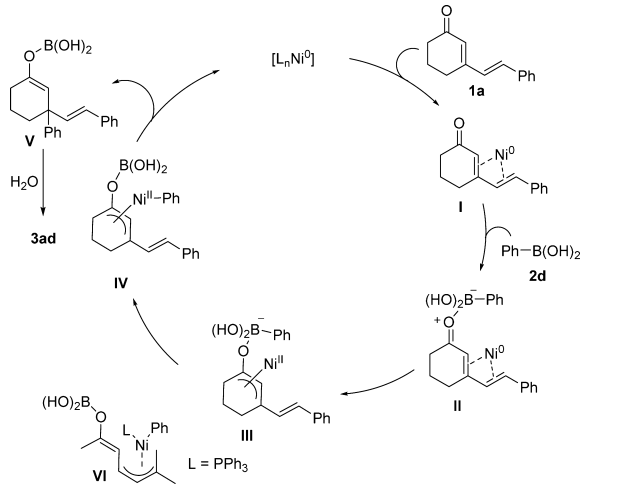
Scheme 3. Ni-Catalyzed Conjugate Addition to Acyclic Dienones



dimethyl substituted dienones **1o** and **1p** reacted with benzeneboronic acid **2d** regioselectively to give 1,4-addition product **3od** in 15% yield and 1,6-addition product **3pd** in 20% yield, respectively (Scheme 3).

A plausible catalytic cycle for the present alkene assisted Ni-catalyzed conjugate addition reaction, based on our experimental observations and known literature,[7−9] is presented in Scheme 4. The catalytic cycle is initiated by the reaction of Ni^0 with dienone **1a** to form η^4-coordinated nickel complex **I**.[7c−f] The boronic acid then acts as a Lewis acid, and the coordination to enone carbonyl oxygen promotes the formation of η^3-allyl complex **III**.[7c−f] Transmetalation of the aryl group leads to the formation of intermediate **IV**. Further reductive elimination regenerates the active Ni^0-complex and a boron enolate product **V**, which provides the final product **3ad** upon hydrolysis.

Scheme 4. A Proposed Reaction Mechanism



The formation of 1,6-addition product **3pd** (Scheme 3) is intriguing in view of the unusual regiochemistry. A Ni-complex (**VI**, Scheme 4), with the η^3-allyl at the β, γ, and δ carbons of the dienone moiety and the coordinated PPh_3 adjacent to the less substituted β carbon and the phenyl substituent close to the more substituted terminal carbon, is proposed as an intermediate for the formation of **3pd**. Reductive elimination affords the final product **3pd**. It is not clear how **VI** is formed. A plausible pathway is that an η^3-allyl Ni-complex similar to intermediate **IV** is formed first and then σ,π-allyl rearrangement gives **VI**.[5d,6c,e]

In conclusion, we have developed a nickel-catalyzed, highly regioselective conjugate addition of boronic acids to dienones to give 1,4-addition products with an all-carbon quaternary center. The presence of a 3-alkenyl substituent assisting the coordination of the dienone substrate to the nickel catalyst center is essential for the substrate to undergo 1,4-conjugate addition. The catalytic reaction is compatible with a variety of aryl- and styrylboronic acids and dienones and does not require any additive for the activation of the boronic acids. Application of the present novel addition reactions to bioactive molecule synthesis and enantioselective synthesis is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures, characterization details, and ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Ministry of Science and Technology of the Republic of China (NSC-102-2628-M-007-005 and NSC-102-2633-M-007-002) for support of this research.

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