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Highly *E*-Selective, Stereoconvergent Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling of Alkenyl Ethers

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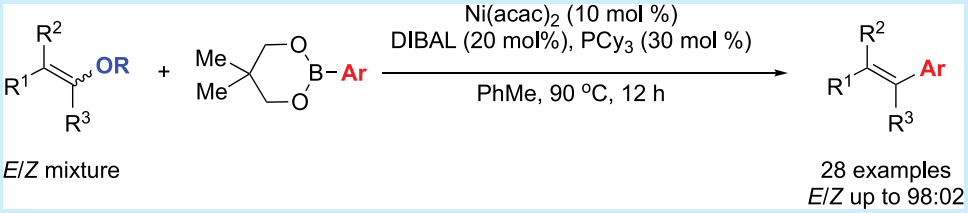
Supporting Information

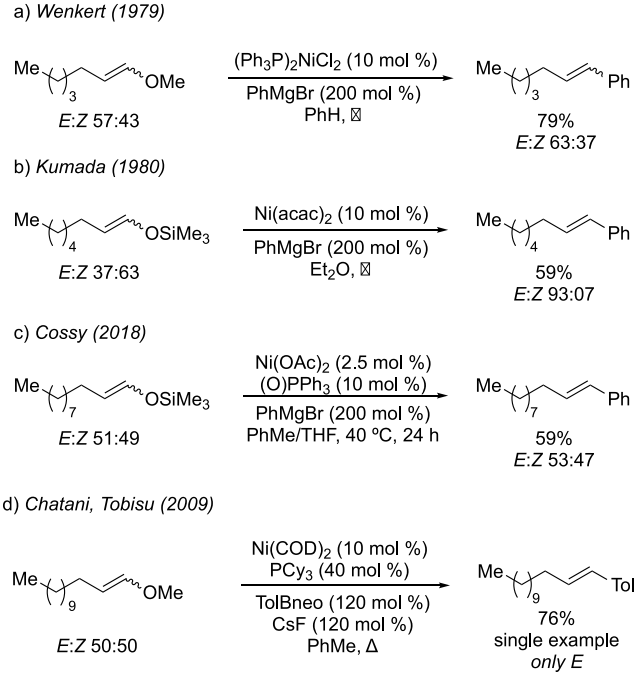


ABSTRACT: An improved method for the nickel-catalyzed Suzuki–Miyaura cross-coupling of alkenyl ethers is reported. This stereoconvergent protocol allows for the utilization of a wide range of alkenyl ethers and aryl boronic esters for the synthesis of variously substituted styrene derivatives. An olefinic mixture with respect to the alkenyl ethers can be employed, thereby circumventing the stereodefined synthesis of starting materials. Preliminary mechanistic investigations indicate a nickel-catalyzed olefin isomerization following initial stereoretentive cross-coupling.

Nickel-catalyzed activations of classically inert bonds have received considerable attention in the last decades.[1] Pioneering studies by Wenkert and others[2] have resulted in the development of practical protocols for the nickel-catalyzed Kumada cross-coupling of various aryl and alkenyl ethers (Scheme 1a–c).[3] In all of these cross-coupling protocols, nickel(II) salts were successfully employed as precatalysts as sacrifical organomagnesium coupling partners led to the in situ formation of the catalytically active species via a transmetalation/reductive elimination. Since these initial findings, milder reaction conditions and broadened substrate scope led to significant improvements,[4] such as the extension of coupling partners from highly reactive organomagnesium to organoboron compounds (Scheme 1d).[5] Despite these contributions, several challenges remain to be addressed and as organoboron coupling partners only sluggishly undergo this cross-coupling reaction, and highly air- and moisture-sensitive $Ni(COD)_2$[6] or laboriously prepared nickel(0) precatalysts have to be employed.[7] Apart from operational challenges, control over double-bond geometry decisively influences the synthetic utility of the present method. Early studies by Chatani and Tobisu have demonstrated that under the reaction conditions the intermediately obtained olefinic mixture of styrenes isomerizes in favor of the thermodynamically more stable *E*-isomer.[5a] This important finding was subsequently briefly examined in the cross-coupling of cyclic alkenyl ethers albeit with limited success.[5e] The authors propose the intermediacy of a Ni–H species to cause olefin isomerization.

We became interested in this topic as part of our ongoing research program combining remote functionalization via chain-walking with various postfunctionalization processes.[8] Recently, we and Mazet have independently reported an efficient combined metal-catalyzed chain-walking/nickel-catalyzed Kumada cross-coupling of alkenyl ether to access a variety of styrene products (Figure 1).[9] During these studies, we realized that the major limitation of this transformation was

Scheme 1. Nickel-catalyzed Kumada and Suzuki-Miyaura cross-coupling of alkenyl ethers



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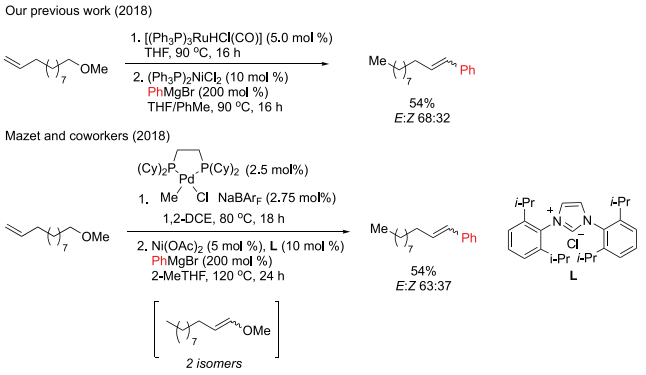


Figure 1. Previously reported tandem metal-catalyzed 'chain-walking'/nickel-catalyzed Kumada cross-coupling.

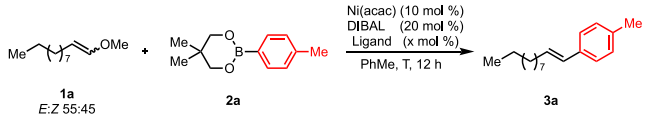
that the moderate *E*/*Z*-selectivity of the enol ether, obtained by isomerization of the double bond, was retained during the cross-coupling event. Based on these findings, we decided to embark on a study and identify conditions that would address this shortcoming, ideally resulting in the development of a mild, stereoconvergent cross-coupling of alkenyl ethers.

At the outset of this study, we wondered whether an in situ generated Ni(0) could successfully promote a stereoconvergent cross-coupling of our model enol ether **1a**, keeping in mind that we were concerned by delineating a new protocol that would be efficient and easy to manipulate with air stable Ni species. As it has been demonstrated that treatment of $Ni(acac)_2$ with DIBAL in the presence of suitable ligands could furnish a range of catalytically active L_nNi species,[10] we were interested in applying those conditions to our transformation. Building on Chatani and Murai's finding of superior reactivity of neopentyl boronic esters,[11] we chose **2a** as the model coupling partner and toluene as the standard solvent (Table 1).

A range of mono- and bidentate ligands were tested under the reaction conditions (Table 1, entries 1−9). Bidentate phosphines, NHC, or bipyridine ligands failed to promote product formation along with sterically demanding Buchwald-type ligand (Table 1, entries 1−7). Only PPh_3 and PCy_3 furnished the desired product in low and high yield, respectively (Table 1, entries 8 and 9). More importantly, PCy_3 provided the product with excellent levels of stereocontrol over the double-bond geometry (*E*/*Z* 96:04). Reducing the catalyst loading (Table 1, entry 10) or utilizing CsF as additive (Table 1, entry 11) results in diminished product formation. Some improvement was achieved by reducing the ligand to metal ratio (Table 1, entry 12). Ultimately, lowering the reaction temperature to 85 °C allowed the isolation of **3a** in 92% yield with an excellent *E*/*Z* ratio (Table 1, entry 13). Further reduction of the temperature to 65 °C resulted in decreased reactivity (Table 1, entry 14).

With the optimal conditions in hand (Table 1, entry 13), we set out to explore the scope of boronic esters as coupling partners (Scheme 2). A wide range of aromatic and heteroaromatic boronic esters delivered the products in usually high yield with excellent control of the double-bond geometry. Electron-withdrawing (Scheme 2, **3d**, **3l**, and **3n**) as well as electron-donating substituents are well-tolerated (Scheme 2, **3h**, **3j**, **3k**, and **3m**). Heteroaromatic moieties, i.e., indole and furan, efficiently undergo the cross-coupling reaction (Scheme 2, entries **3m** and **3o**) albeit in lower yield in the latter case, most probably due to insufficient stability under the reaction

Table 1. Optimization of Nickel-Catalyzed Suzuki-Miyaura Cross-Coupling of Alkenyl Ether 1a[a]



1a *E*:*Z* 55:45 + 2a → 3a

entry	ligand (mol %)	*T* (°C)	3a[b] (%)	*E*/*Z*[c]
1	dcype (20)	105	nr	nd
2	dcypf (20)	105	nr	nd
3	dppe (20)	105	nr	nd
4	Xantphos (20)	105	nr	nd
5	ICy·HBF_4 (40)	105	nr	nd
6	6,6′-Me_2-2,2′-pyridine (20)	105	nr	nd
7	SPhos (40)	105	nr	nd
8	PPh_3 (40)	105	25	85:15
9	PCy_3 (40)	105	86	96:04
10[d]	PCy_3 (20)	105	62	95:05
11	PCy_3 (40)[e]	105	60	95:05
12	PCy_3 (30)	105	90	95:05
13	***PCy_3 (30)***	**85**	**92**[f]	***97:03***
14	PCy_3 (30)	60	57	96:04

[a]All reactions were carried out using **1a** (0.27 mmol) and **2a** (0.32 mmol, 120 mol %) in 1.4 mL of toluene. [b]Yields determined by analysis of the unpurified mixture of products by ^1H NMR with an internal standard in chloroform-*d*. [c]Ratio determined by analysis of the unpurified mixture of products by ^1H NMR. [d]$Ni(acac)_2$ (5.0 mol %), DIBAL (10 mol %). [e]CsF (120 mol %). [f]Yields of isolated products after purification by column chromatography.

conditions. Interestingly, when various anisole derivatives were used as coupling partners, no subsequent cross-coupling products were observed on the aromatic ring (Scheme 2, **3h** and **3i**). Steric hindrance resulted in slightly diminished *E*/*Z* ratios (Scheme 2, **3c** and **3g**). Additional steric bulk resulted in no product formation (Scheme 2, reactant **2p**) in addition to boronic esters possessing either a nitro, pyridine, or thiophene unit (Scheme 2, reactant **2q**−**t**).

With these encouraging results in hand, we then explored the scope of alkenyl ethers as coupling partners with **2a** as a model boronic ester. To this end, a variety of cyclic and acyclic alkenyl ethers were subjected to the previously optimized reaction conditions (Table 2). Simple acyclic alkenyl ethers cleanly furnished the products in good to high yield with excellent *E*/*Z* ratios (Table 2, entries 1−6). Additional degrees of unsaturation were well-tolerated given that the olefin is embedded within a trisubstituted olefin (Table 2, entry 4), but less-substituted olefins undergo a well-precedented nickel-catalyzed chain-walking, giving rise to a mixture of isomers along with partial reduction product (Table 2, entry 3). Nevertheless, the efficiency of the projected cross-coupling remained unaffected, and the products were obtained in excellent combined yield as virtually single geometrical isomers. The same phenomenon of partial isomerization of the double-bond was also observed in the case of the sensitive enol ether **1g** (Table 2, entry 6), which provided a mixture of two styrene products. This result further advocates the notion of a nickel-mediated olefin isomerization following the cross-coupling event.

Cyclic enol ether **1h** could be converted successfully into linear alkenol **3v** in good yield with reasonable control over the double-bond geometry (Table 2, entry 7). Interestingly, the corresponding six-membered alkenyl ether failed to undergo

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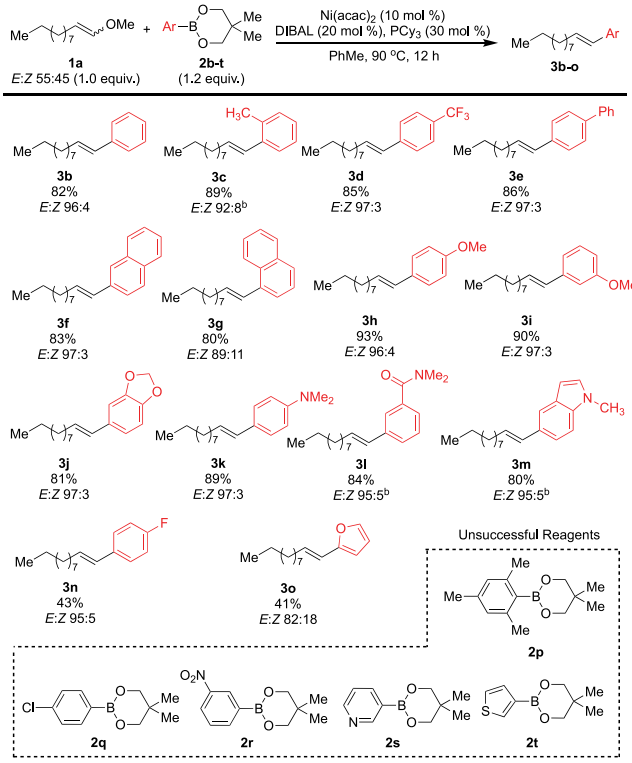
Scheme 2. Cross-Coupling of Alkenyl Ether 1a with Different Boronic Esters[a]



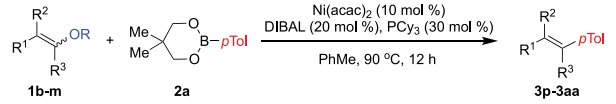
[a]All reactions were carried out using **1a** (0.27 mmol) and **2b−t** (0.33 mmol, 120 mol %) in 1.4 mL of toluene. Yields were individually obtained after purification by column chromatography on silica gel. The *E*/*Z* ratio was determined by ^{1}H NMR spectroscopic analysis of the unpurified mixture of products. [b]The reaction was carried out at 105 °C.

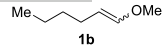
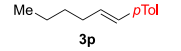
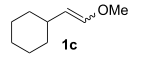
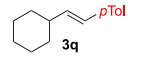
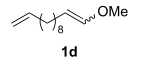
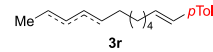
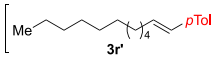
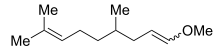
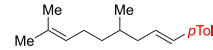
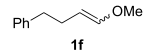
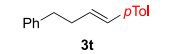
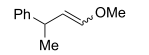
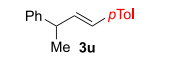
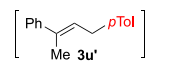
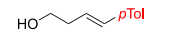
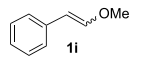
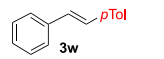
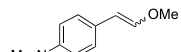
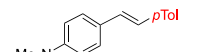
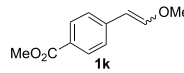
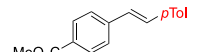
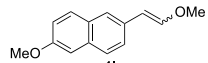
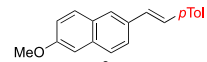
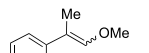
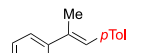
the desired transformation (see the Supporting Information). Alkenyl ethers bearing an aromatic moiety finally provided access to variously substituted stilbenes in good yields and excellent *E*/*Z* ratios (Table 2, entries 8−11). As expected, trisubstituted olefin **1m** only partially underwent isomerization, furnishing the product with a low *E*/*Z* ratio (Table 2, entry 12).

Having established a robust protocol for the transformation of a variety of alkenyl ethers and boronic esters into substituted styrenes and stilbenes, we decided to test the applicability of this method to the synthesis of biologically relevant molecules. At the outset, a scale-up experiment established our confidence in the robustness of the current method (Scheme 3a). Subsequently, the synthesis of DMU-212, a resveratrol analogue with potential anticancer properties for the treatment of human ovarian cancer,[12] was successfully executed (Scheme 3b).

In order to gain additional insight into this intriguing double-bond isomerization process, a series of control experiments were designed (Table 3). To this end, *Z*-**3p** was independently synthesized and exposed to our established reaction conditions (Table 3, entry 1). It was found that under standard conditions, complete double-bond isomerization took place. The same result was obtained in the absence of boronic ester coupling partner **2a** (Table 3, entry 2) and even without ligand (Table 3, entry 3). From the above presented results it appears reasonable to assume that a nickel hydride may

Table 2. Cross-Coupling of Boronic Ester 2a with Different Alkenyl Ethers 1b−m



entry	substrate	E:Z	product	yield	E:Z
acyclic enol ethers					
1	 **1b**	51:49	 **3p**	82%	95:05
2[b]	 **1c**	67:33	 **3q**	72%	95:05
3	 **1d**	54:46	 **3r**	79%	95:05
			 **3r'**	12%	97:03
4[b]	 **1e**	55:45	 **3s**	77%	96:04
5	 **1f**	58:42	 **3t**	90%	96:04
6[b]	 **1g**	60:40	 **3u**	61%	> 95:05
			 **3u'**	10%	> 95:05
cyclic enol ether					
7	 **1h**	--	 **3v**	62%	89:11
styrenyl enol ethers					
8	 **1i**	55:45	 **3w**	81%	> 95:05
9	 **1j**	40:60	 **3x**	88%	> 95:05
10[b]	 **1k**	30:70	 **3y**	45%	> 95:05
11	 **1l**	65:35	 **3z**	78%	> 95:05
12[c]	 **1m**	55:45	 **3aa**	72%	68:32

[a]All reactions were carried out using **1b−m** (0.27 mmol) and **2a** (0.33 mmol, 120 mol %) in 1.4 mL of toluene. Yields were individually obtained after purification by column chromatography on silica gel. The *E*/*Z* ratio was determined by ^{1}H NMR spectroscopic analysis of the unpurified mixture of products. [b]Reaction was carried out at 105 °C. [c]Reaction was carried out using Ni(acac)$_2$ (20 mol %), DIBAL (40 mol %), and PCy$_3$ (60 mol %) in 1.4 mL of toluene at 105 °C.

intermediately be formed, which causes double-bond isomerization or migration (Table 2, entry 3). Indeed, in the absence of DIBAL, no olefin isomerization of *Z*-**3p** was observed and only starting material was retrieved (Table 3, entry 4). To rule out a thermal process, the reaction was conducted at 60 and 25 °C in the presence of DIBAL and Ni catalyst (Table 3, entries 5−7). In both cases, *E*-**3p** was obtained as a single geometrical isomer, therefore excluding a thermally induced process. It should be noted that the pure thermal treatment of *Z*-**3p** does not produce the *E*-isomer either. These results support the

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Scheme 3. Scale-up Experiment of 3a and Synthesis of Potential Anticancer Agent DMU-212 (3ab)

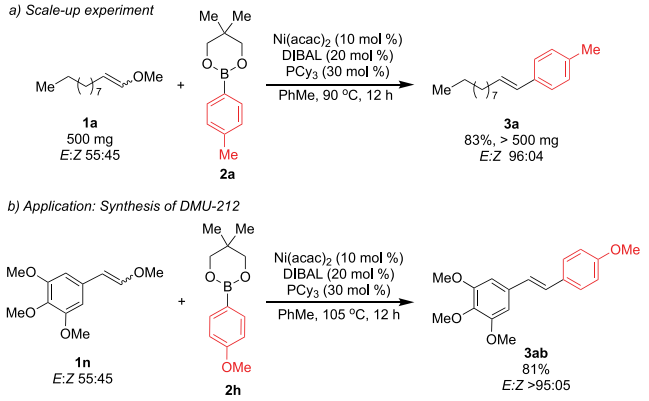
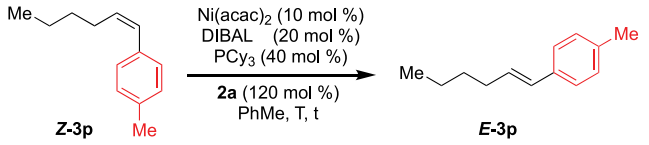
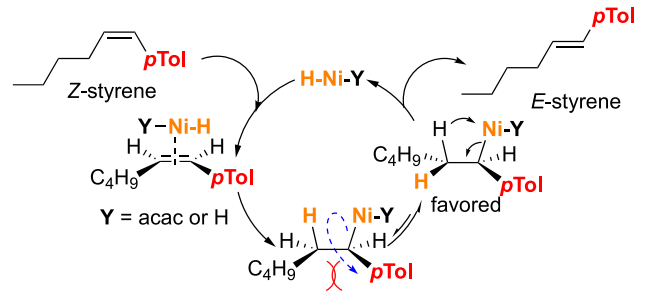


Table 3. Control Experiments To Identify Isomerization-Active Species[a]



entry	[Ni]	DIBAL	PCy3	2a	T (°C)	time (h)	E/Z
1	√	√	√	√	105	16	98:02
2	√	√	√	×	105	16	96:04
3	√	√	×	×	105	16	95:05
4	√	×	×	×	105	16	n.r.
5	√	√	×	×	60	16	>95:05
6	√	√	×	×	25	48	>95:05

[a]All reactions were carried out using *Z*-**3p** (0.27 mmol) and, if applicable, **2a** (0.33 mmol, 120 mol %) in 1.4 mL of toluene. The *E*/*Z* ratio was determined by ^{1}H NMR spectroscopic analysis of the crude mixture.



conclusion that olefin isomerization ensues the cross-coupling process to provide a stereoconvergent protocol. We are proposing the presence of a nickel hydride promoting the isomerization process through an addition−elimination sequence (see the graphic below Table 3) that is also in good agreement with the results described in Table 2, entry 3, where olefin isomerization was observed.

In conclusion, we have established a user-friendly, operationally simple protocol for the stereoconvergent nickel-catalyzed cross-coupling of olefinic mixtures of alkenyl ethers with aromatic boronic esters. The utilization of easy-to-handle $Ni(acac)_2$ as a precatalyst along with DIBAL as reductant provides a simple way to access a highly active nickel catalyst in situ. A broad array of variously functionalized styrenes and stilbenes could be accessed in good to high yields with generally excellent control over the double-bond geometry. Various aromatic and heteroaromatic boronic esters could be successfully employed in this transformation. Both acyclic and cyclic alkenyl ethers participated well in this process comprising Lewis basic groups or additional degrees of unsaturation. Mechanistic investigations led us to propose that the olefin isomerization is subsequent to the cross-coupling reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00946.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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