Mizoroki–Heck Chemistry

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Nickel-Catalyzed Mizoroki–Heck Reaction of Aryl Sulfonates and Chlorides with Electronically Unbiased Terminal Olefins: High Selectivity for Branched Products**

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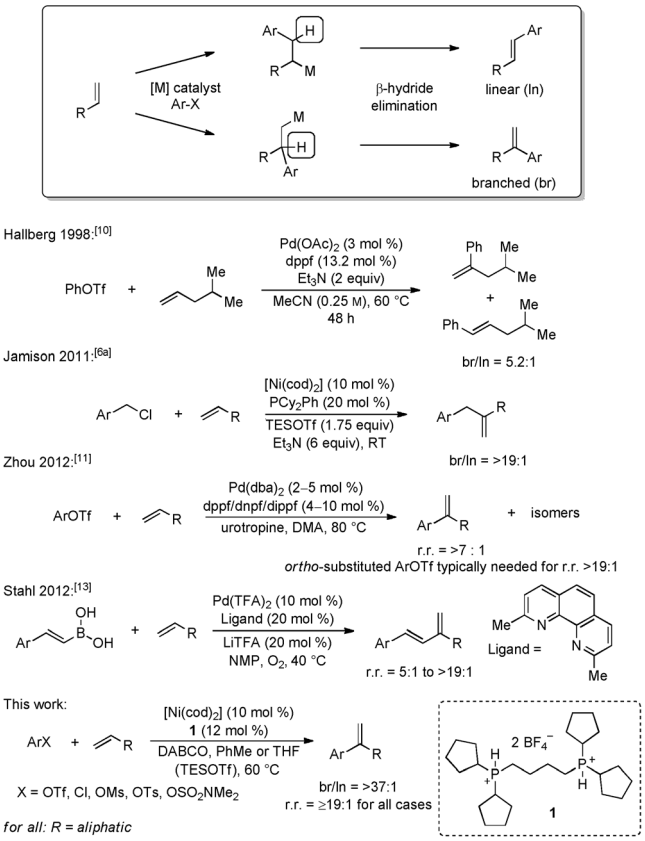
Abstract: *Achieving high selectivity in the Heck reaction of electronically unbiased alkenes has been a longstanding challenge. Using a nickel-catalyzed cationic Heck reaction, we were able to achieve excellent selectivity for branched products (≥ 19:1 in all cases) over a wide range of aryl electrophiles and aliphatic olefins. A bidentate ligand with a suitable bite angle and steric profile was key to obtaining high branched/linear selectivity, whereas the appropriate base suppressed alkene isomerization of the product. Although aryl triflates are traditionally used to access the cationic Heck pathway, we have shown that, by using triethylsilyl trifluoromethanesulfonate, we can effect a counterion exchange of the catalytic nickel complex, such that cheaper and more stable aryl chlorides, mesylates, tosylates, and sulfamates can be used to yield the same branched products with high selectivity.*

Since the 1970s, the Mizoroki–Heck reaction[1] has afforded synthetic chemists a powerful way to synthesize more substituted olefins from aryl or benzyl electrophiles and simpler alkenes.[2] Although much less well studied than its Pd-catalyzed counterpart, the Ni-catalyzed Heck reaction[3] can offer several distinct advantages in addition to the low cost of nickel, including: faster oxidative addition (allowing for the use of a wide range of electrophile classes), more facile olefin insertion, and a more controlled steric environment owing to shorter Ni-ligand bond lengths.[4] These advantages seem to be underutilized in the Heck reaction, compared to the more prevalent use of Ni in other cross-coupling reactions.[5] Recently, our group demonstrated some of these features by showing that benzyl chlorides could react with ethylene and terminal olefins in a highly selective manner (≥ 19:1 in most cases) to afford branched products using $[Ni(cod)_2]$ and PCy_2Ph (cod = 1,5-cyclooctadiene, Cy = cyclohexyl).[6] This report represented the first example of a catalyst-controlled, highly branched-selective Heck reaction of electronically unbiased alkenes. Herein, we report the expansion of this highly regioselective reaction to more widely used aryl electrophiles.



Scheme 1. Branched-selective Heck reactions.

For terminal alkenes, there are two possible regiochemical outcomes of the Heck reaction (Scheme 1). Classically, electron-poor olefins have been utilized for Heck couplings, yielding almost exclusively linear products. However, by the mid-1990s, a series of developments by Cabri and Candiani,[7] as well as others,[8] allowed access to the cationic Heck pathway to provide high selectivity for branched products with electron-rich olefins. By manipulation of the reaction conditions, counterion dissociation from the metal center is favored, which can cause a reversal in overall branched/linear (br/ln) selectivity.[9]

Unfortunately, electronically unbiased olefins have given more modest br/ln ratios (e.g. 5.2:1), even under cationic conditions.[10] In the past year, this field has seen renewed interest. Zhou and co-workers reported the Pd-catalyzed Heck reaction of terminal olefins[11] and vinylarenes[12] with

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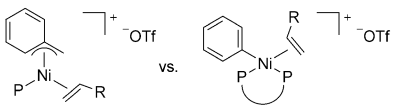


Figure 1. Key intermediate structures for benzyl (left)[6a] and aryl (right) electrophiles in the cationic Heck mechanism.

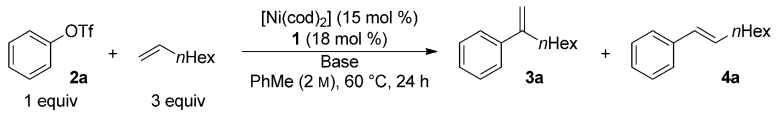
aryl triflates in good yields. Stahl and co-workers also reported the oxidative Heck reaction of vinyl boronic acids and terminal olefins using Pd and a phenanthroline-type ligand.[13] In these reactions, high levels of regioselectivity for a wide substrate scope are of the utmost importance, as in nearly all cases the resulting alkene regioisomers are inseparable by column chromatography.[14] However, the work from the Zhou and Stahl groups displays a wide range of regioselectivities, with the former method typically needing *ortho*-subsituted aryl triflates to achieve excellent levels of regioselectivity (defined here as $\geq$19:1, i.e. $\geq$95:5).

Building on our understanding of the Ni-catalyzed cationic Heck reaction,[6a,15] we set out to directly access this pathway with phenyl triflate (**2a**) and 1-octene. The ligand previously used for benzyl chlorides, PCy_2Ph (**5**), produced only a moderate yield and regioisomeric ratio (r.r.) of the desired product, even after optimization of reaction conditions (Table 1, entry 1). Comparing the proposed intermediates in Figure 1, we see that a benzyl electrophile can transition from η^1 to η^3.[6a] However, the ligand sphere for aryl electrophiles is quite different, presumably containing two ligated phosphines, and providing a fresh challenge for inducing high levels of regiocontrol. Extensive investigation of monodentate ligands of varying electronic and steric properties provided little improvement in yield or br/ln selectivities; thus, the search was expanded to bidentate ligands. Dcypp (**6**) demonstrated excellent regioselectivity, but only moderate reactivity (entry 2). Elevated temperatures led to formation of visible nickel(0) particles and deterioration of yields. We hypothesized that, while oxidative addition proceeded smoothly, insertion of the phenyl group to the alkene remained slow. In order to promote this step, we investigated ligands of a wider bite angle, as larger bite angles have been shown, both theoretically[16] and experimentally,[17] to increase the rate of migratory insertion.

Indeed, bidentate ligands with larger bite angles[18] such as dippf (**7**) increased conversion and were more stable at higher temperatures (entry 3). A four-carbon bridge seemed most promising overall. Dcypb (**10**) showed low conversion at room temperature, but was stable at 60 °C, providing excellent br/ln product ratios, good yields, and no formation of side products (entry 6). Use of cyclopentyl rather than cyclohexyl groups in the ligand (**1**) provided the best results with high conversion, excellent br/ln selectivity, and good overall r.r. (entry 7). Finally, if a persistent Ni–H species is responsible for erosion of the r.r. of the product after β-H elimination, changing the base might decrease isomerization. Gratifyingly, 1,4-diazabicyclo[2.2.2]octane (DABCO) provided superior yields and regioselectivities, and additionally allowed reduction of the catalyst loading to 10 mol% (entry 8). Furthermore, the amount of 1-octene necessary in the reaction could be reduced to 1.5 equiv or even to 1.1 equiv (entry 9), making this transformation attractive for reactions in which both reaction components are valuable.

Even more significantly, the combination of DABCO and ligand **1** allowed the use of aryl chlorides for the first time (Table 2). Although our group had previously demonstrated that TESOTf could be used to perform a counterion exchange of Ni–Cl to Ni–OTf for benzyl chlorides in order to enter the cationic Ni-Heck pathway, previous attempts to use aryl chlorides had failed. But, with some modification of reaction conditions, good yields of product **3a** could be obtained, not only for aryl chlorides (entry 1), but also aryl mesylates (entry 2), tosylates (entry 3), and sulfamates (entry 4).[19] Although bromides and iodides underwent oxidative addition, counterion exchange did not occur. This use of electrophiles that are traditionally viewed as unreactive with Pd demonstrates the power of Ni-catalyzed reactions to access products made from less expensive, more stable, and more readily available chlorides and phenol derivatives.[5]

Table 1: Ligand optimization: tether length and steric demand.



Entry	Ligand	Natural bite angle [°][a]	Base (equiv)	T [°C]	Conversion [%][b]	Yield [%][c]	br/ln	r.r.[d]
1[e]	PCy_2Ph (**5**)	–	Et_3N (3)	RT	87	47	11.4:1	2.7
2	dcypp (**6**)	104	Et_3N (3)	RT	20	22	>100:1	9.9
3[e]	dippf (**7**)	120	Et_3N (3)	60	50	41	>100:1	9.8
4	diop (**8**)	105	Et_3N (3)	RT	86	70	5.2:1	2.8
5	dppb (**9**)	102	Et_3N (5)	RT	65	48	7.2:1	2.8
6	dcypb (**10**)	111	Et_3N (5)	60	68	67	>100:1	9.2
7	ligand **1**	107	Et_3N (5)	60	89	86	>100:1	7.5
8[f]	ligand **1**	107	DABCO (3)	60	>95	99[g]	87:1	32.9
9[h]	ligand **1**	107	DABCO (3)	60	94	92	>100:1	36.5

[a] Calculated according to Ref. [18] using molecular mechanics MMF force field and a Ni–P bond length of 2.28 Å. [b] GC conversion with respect to PhOTf. [c] Yield of branched product **3a** only, as determined by GC analysis. [d] Ratio of br/all isomers. [e] Ligand (30 mol%). [f] $[Ni(cod)_2]$ (10 mol%), **1** (12 mol%), 1-octene (1.5 equiv), THF (1 M). [g] Yield of isolated product. [h] 1-octene (1.1 equiv). cod = 1,5-cyclooctadiene, DABCO = 1,4-diazabicyclo[2.2.2]octane.

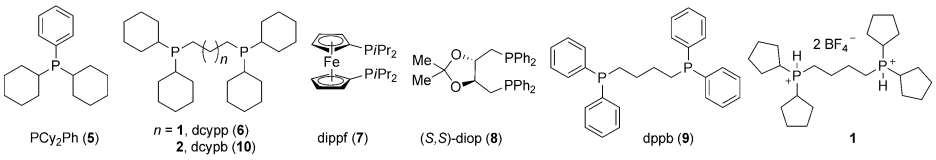


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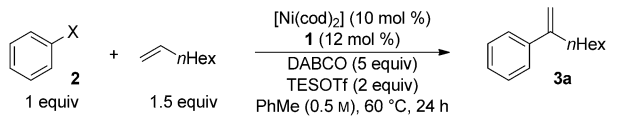
Table 2: Reaction of aryl halides and sulfonates with TESOTf.[a]



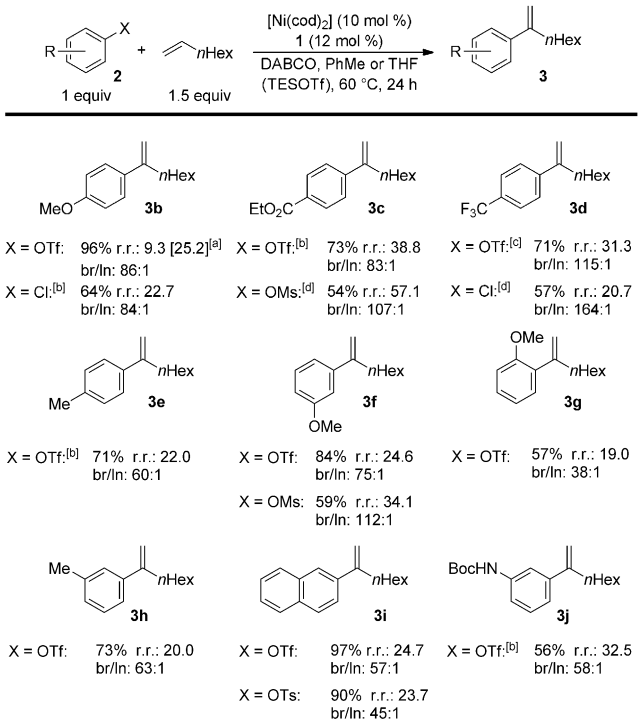
Entry	X	Yield [%]	br/ln	r.r.[b]
1	Cl	81	62:1	35.7
2	OMs	91	60:1	30.4
3	OTs	72	37:1	19.6
4	OSO_2NMe_2	61	59:1	19.6
5	Br	4[c]	–	–
6	I	2[c]	–	–

[a] All yields shown are of isolated products, unless otherwise noted. [b] Ratio of br/all isomers. [c] Yield determined by GC analysis. Ms = methanesulfonyl, Ts = *para*-toluenesulfonyl.

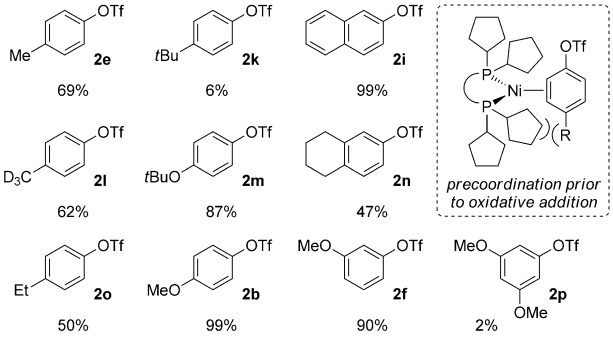
With these optimized conditions in hand, we sought to explore the scope of this transformation. A range of substituted aryl electrophiles were subjected to the reaction conditions (Scheme 2). A variety of substituents were tolerated, from electron-rich (**3b**) to electron-poor (**3c**, **3d**), with electron-poor substrates providing slightly slower reaction rates, but excellent regioselectivities. Very electron-rich products, however, were prone to isomerization upon purification. Therefore, regioselectivities are reported before and after purification for **3b** and **3t**.[20] Gratifyingly, reactions involving counterion exchange with TESOTf to access the cationic intermediate worked only slightly less efficiently than simply beginning with the aryl triflate. Substitution at the *para*- and *meta*-positions was, for the most part, also well tolerated. *Ortho*-substitution resulted in lower yield and a slightly reduced r.r. (**3g**).

Although the electrophile scope was broad, we found that substrates with *para*-alkyl groups (**2e**) suffered from reduced yields and required longer reaction times. This puzzling observation did not seem to stem from the presence of benzylic C–H bonds, as *para*-*t*BuPhOTf (**2k**) resulted in almost no conversion, suggesting a steric phenomenon. Nakamura and co-workers have proposed an explanation for just such an effect: the rate-limiting precoordination of the least hindered portion of the arene, which forms a π-complex prior to oxidative addition, for Ni-catalyzed cross-coupling reactions.[4,21] We sought to explore this mechanistic feature further by preparing a variety of *para*-substituted aryl triflates and subjecting them to the reaction conditions (Scheme 3). Overall, the results are consistent with steric crowding of the ligand cyclopentyl groups and the group in the *para*-position. Substrates with groups in the *meta*-position (**2f**, **2h**) can coordinate on the less sterically hindered side of the arene, and react more quickly than those with *para*-substituents (as also observed by Nakamura). However, when two *meta*-substituents (**2p**) are introduced, the substrate can no longer coordinate well, and the reaction does not proceed.

A range of aliphatic alkenes also successfully underwent the desired transformation (Scheme 4), again using triflates or chlorides/sulfonates with TESOTf. The presence of increased steric bulk at the allylic position was well tolerated, although extended reaction times were needed (**3r**). Protected alcohol



Scheme 2. Scope of aryl electrophile with 1-octene. All yields shown are of isolated products. Reaction conditions: for X = OTf: $[Ni(cod)_2]$ (10 mol%), **1** (12 mol%), DABCO (3 equiv), THF (1 M), 60°C, 24 h. For X = Cl, OMs, OTs: $[Ni(cod)_2]$ (10 mol%), **1** (12 mol%), DABCO (5 equiv), TESOTf (2 equiv), PhMe (0.5 M), 60°C, 24 h. [a] r.r. before purification. [b] 48 h. [c] $[Ni(cod)_2]$ (15 mol%), **1** (18 mol%), 1-octene (3 equiv), 48 h. [d] TIPSOTf (2 equiv), 48 h. br/ln = ratio of **3** to linear product **4** (GC), r.r. = ratio of **3** to all other isomers, mainly olefin isomerization (GC). TIPS = triisopropylsilyl.



Scheme 3. Investigation of steric substitution effects. Results shown are the conversion of triflate under standard conditions (24 h), as determined by GC analysis.

and amine functional groups were compatible (**3t**, **3u**), although the presence of acidic protons (such as free alcohols or ketones with enolizable protons) in the alkene led to complete inhibition of the reaction. The transformation was selective for terminal olefins in the presence of more substituted alkenes (**3s**).

In summary, we have successfully developed a Ni-catalyzed Mizoroki–Heck coupling of aryl triflates, chlorides, and

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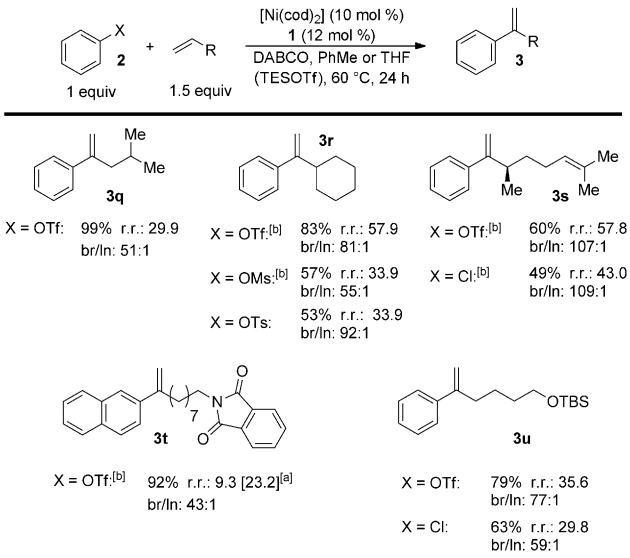

Scheme 4. Scope of the alkene coupling partner. All yields shown are of isolated products. Reaction conditions: for X = OTf: $[Ni(cod)_2]$ (10 mol%), **1** (12 mol%), DABCO (3 equiv), THF (1 M), 60 °C, 24 h. For X = Cl, OMs, OTs: $[Ni(cod)_2]$ (10 mol%), **1** (12 mol%), DABCO (5 equiv), TESOTf (2 equiv), PhMe (0.5 M), 60 °C, 24 h. [b] r.r. before purification. [c] 48 h. br/ln = ratio of **3** to linear product **4** (GC), r.r. = ratio of **3** to all other isomers, mainly olefin isomerization (GC).

other sulfonates with electronically unbiased alkenes in good yields. This reaction displays excellent branched/linear selectivity for the coupled product, with overall regioselectivities (of the desired product to all other isomers) that are $\geq$ 19:1 in all cases. This universally highly branched-selective Heck reaction also leverages the intrinsic properties of Ni to allow for the use of inexpensive, stable, and synthetically practical chlorides and sulfonates as coupling partners. Though the cost of $[Ni(cod)_2]$ is not insignificant, we hope to continue to develop alternative catalysts or precatalysts from inexpensive Ni sources.[6b,22] These developments continue to show the promise of the Ni-catalyzed Heck reaction as a viable, highly selective alternative to its Pd-catalyzed counterpart.

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