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The catalytic enantioselective Birch-Heck sequence for the synthesis of tricyclic structures with all-carbon quaternary stereocenters

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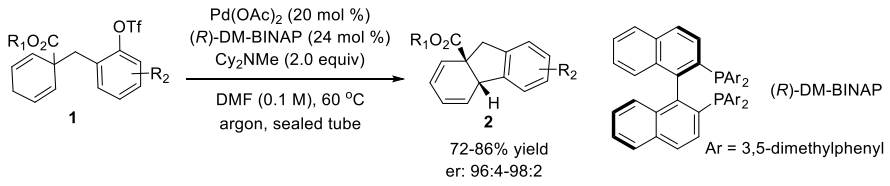
Supporting Information Placeholder



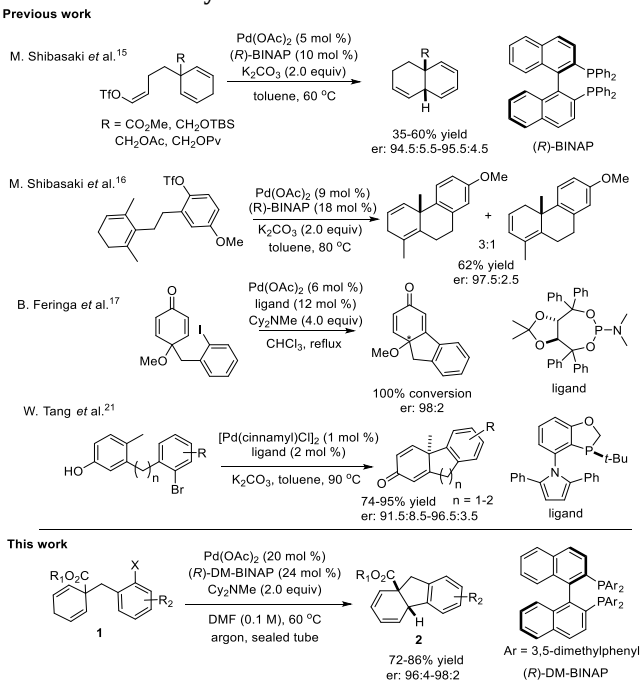
ABSTRACT: A new enantioselective desymmetrizing Mizoroki-Heck reaction is reported. The process affords high yields and enantioselectivities of tricyclic structures containing all-carbon quaternary stereocenters. The substrates for the reaction are efficiently synthesized from Birch reduction-alkylation of benzoic acid and benzoate esters.

Recent structural analysis of drug candidates has discovered that successful drugs have a higher percent of sp^3 carbons and are more likely to contain stereogenic centers. In a series of articles entitled "Escape from Flatland,"[1, 2] Lovering and colleagues analyzed drug development candidates since 1980 and discovered a higher frequency of sp^3 carbons and chiral centers in successful drugs. Two reasons have been advanced to explain the better pharmaceutical profile of sp^3 rich and chiral molecules: improved solubility[2] and less promiscuous binding behavior[1].

In contrast to the apparent need for drug candidates with sp^3 carbons and chiral centers, the three most commonly used reactions by medicinal chemists remain amide bond formation, the Suzuki-Miyaura reaction and nucleophilic aromatic substitution[3]. These sp^2 carbon-focused methodologies in combination with other popular and efficient cross coupling synthetic tools have likely contributed to the preponderance of flat aromatic structures in compound screening libraries. To overcome this limitation and assist in the development of better drug candidates, there is a pressing need for more efficient tools to construct chiral, non-planar structures.

One of the most challenging sp^3 stereocenters to construct is the all-carbon quaternary center[4-7]; and one popular and efficient method for creating quaternary all-carbon stereocenters is the Mizoroki-Heck (Heck) reaction[8]. Many elegant enantioselective applications of the Heck reaction have been described[9-11], but the full substrate scope of the asymmetric Heck reaction has yet to be explored, and important tools for the construction of complex bioactive structures remain to be developed. A recent popular approach to more general enantioselective Heck reactions involves desymmetrization reactions[5, 12-14]. Scheme 1 illustrates a collection of examples related to the current work, including desymmetrization examples by Shibasaki[15, 16] and Feringa[17, 18]. These procedures demonstrated modest to good yields and high enantioselectivities to polycyclic ring structures, which are common components of successful drugs[19, 20].

Scheme 1. Catalytic enantioselective Heck reactions.

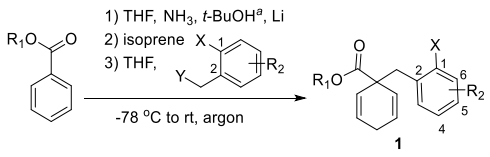


Herein, we report a new desymmetrizing enantioselective Heck reaction, which has both high yields and enantioselectivities. The method complements recent work by Tang[21] and Feringa, and expands the scope of the Shibasaki work being both more efficient and more stereoselective. In the process, a

tricyclic ring system is generated with an all-carbon quaternary stereocenter. In addition, the substrates are produced through an efficient Birch reduction-alkylation process with inexpensive benzoic acid or benzoate esters. Although this process is perfectly suited to the facile generation of cyclohexadiene desymmetrization substrates, previous work has almost exclusively used alkylation of the considerably more expensive 2,5-cyclohexadiene-1-carboxylic acid[15] or a 5-6 step sequence starting with cyclohexenone derivatives[22-25].

Our study began with the synthesis of various substrates using the Birch reduction-alkylation reaction (Table 1)[26]. Both benzoic acid and benzoate ester substrates were used. With benzoate esters, *t*-BuOH is added as a proton source to protonate the radical anion intermediate. In all cases, a 2-iodo or 2-triflate group was incorporated in the alkylating agent for later use in the Heck reaction. The Birch reduction-alkylation yields generally ranged from good to excellent with the 2-iodo derivatives affording the highest yields (entry 1 and 7). The lowest yielding examples involved alkylating agents with 2-triflate and substituted benzene rings (entry 3 and 6). In these cases, there was considerable decomposition, including, not surprisingly, from cleavage of the triflate group. Although benzyl bromides were the alkylating agent of choice, we found the benzyl chloride better in some cases, including with benzoic acid reductive alkylations (entry 9) or in cases where the triflate alkylating agent proved unstable as a benzyl bromide derivative (entry 6). Notably the benzyl halides used in the Birch reaction are some of the most complex used to date and the first example of an alkylating agent with an aryl triflate.

Table 1. Birch reduction-alkylation reaction.

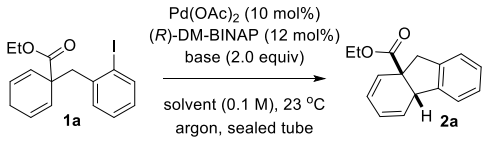


entry	R_1	X	Y	R_2	yield (%)	compd
1	Et	I	Br	H	85	1a
2	Et	OTf	Br	H	54	1b
3	Et	OTf	Br	4-Me	18	1c
4	Et	OTf	Br	5-Me	78	1d
5	Et	OTf	Br	6-Me	77	1e
6	Et	OTf	Cl	4-Cl	28	1f
7	*t*-Bu	I	Br	H	96	1g
8	*t*-Bu	OTf	Br	H	79	1h
9	H	OTf	Cl	H	57	1i

[a] *t*-BuOH added with benzoate ester substrates

Initial Heck reaction studies were conducted with the 2-iodo substrates (Table 2), as they were more readily synthesized through the Birch reduction-alkylation. Extensive reaction screening was conducted to optimize ligands, bases, solvents and temperatures. Table 2 illustrates modifications to solvents, bases, Ag_2CO_3 equivalents, and reaction concentration, which lead to some of the more successful efforts. The Supporting Information (SI) has a complete account of the reaction screening. The reactions did afford efficient conversions (50-90% yields) and the use of toluene or 1,4-dioxane with Ag_2CO_3 afforded the 1,3-diene product exclusively (cf. Table 3 products). This was critical as, not surprisingly, the diene isomers had almost identical chromatographic properties and therefore the presence of both made enantioselectivity evaluations difficult. An additional challenge was found with incomplete reactions as the iodo starting materials had similar chromatographic properties to the cyclized products. Nonetheless, despite significant optimization efforts, the best enantioselective ratio achieved was 88:12 (entry 5 and 10). It should be noted that in this and all subsequent examples, the cis ring junction isomers were presumed to be formed, but the exact enantiomer has not been determined.

Table 2. Aryl iodide Heck reaction optimization.



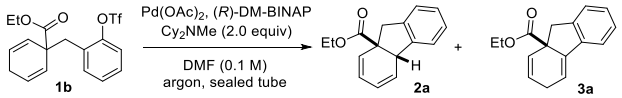
entry	solvent	base	time (h)	result	er
1	DMF	Ag_2CO_3	118	no rxn.	-
2	toluene	Ag_2CO_3	137	2a	79:21
3	1,4-dioxane (0.05 M)	Ag_2CO_3	280	2a	84:16
4	1,4-dioxane (0.2 M)	Ag_2CO_3	67	2a	81:19
5	1,4-dioxane	Ag_2CO_3	137	2a	88:12
6	1,4-dioxane	Ag_2CO_3 (1.0 equiv)	1000	inc.[a]	-
7	1,4-dioxane	Ag_2CO_3 (4.0 equiv)	87	2a	87:13
8	1,4-dioxane	Na_2CO_3[b]	153	2a	75:25
9	1,4-dioxane	Cy_2NMe[b]	87	2a	81:19
10[c]	1,4-dioxane	Ag_2CO_3	137	2h	88:12

[a] incomplete; [b] 2.0 equiv Ag_3PO_4 added as halide scavenger; [c] *t*-Bu ester used

Although aryl halides have been successful in affording enantioselective Heck reactions (Scheme 1, Feringa and Tang work), there is good evidence that the most reliable path to high enantioselectivities in asymmetric Heck reactions is via a cationic palladium complex pathway[10, 11]. Cationic palladium complex formation was promoted with the aryl iodides through the use of silver salts (Table 2), however, we had reached a limit to the enantioselective gains from the silver. Consequently, we turned to aryl triflates, whose counteranion is much weaker than the halides and does not require silver salt sequestration to provide greater amounts of cationic palladium complex. Table 3 details the exploratory work with aryl triflates which lead to the first reaction examples with enantioselectivities exceeding 90%. Although 1,4-dioxane was the optimal solvent for the aryl iodide reactions, DMF worked best for the aryl triflates and, as a strong coordinating solvent, could provide cationic palladium complex stabilization[27, 28]. Without the need for silver in the Ag_2CO_3 base, Cy_2NMe was determined to be the optimal base. One additional fortunate outcome of the aryl triflate substrates was the exclusive formation of the 1,3-diene product in most all cases. As noted for Table 2 results, incomplete reactions were difficult to analyze due to the similar chromatographic properties of the triflate starting materials and the cyclized product. Although efforts

were made to reduce the Pd catalyst equivalents, lower amounts resulted in slower or incomplete reactions (cf. entries 4 and 5 versus 6). While increasing the reaction temperature to accelerate the process degraded the enantioselectivity (cf. entry 9 versus 10 and 11); this is likely because it compromised the stability of the palladium-BINAP complex. Higher catalyst loadings for aryl triflate reactions with stable diphosphine bidentate ligands are relatively common[29-31]. These ligands form stable complexes, which critically and thoroughly control the chiral environment of the catalytic complex, but frequently lead to slow turnover in the process.

Table 3. Aryl triflate Heck reaction optimization.



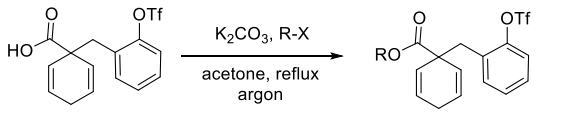
1b 2a 3a

entry	cat. (mol %)	temp (°C)	time (h)	result	er
1	10	23→100	229	no rxn.	-
2	10	23	215	2a/3a (68:32)	-
3	10	23	21	no rxn.	-
4	10	40	593	inc.[a]	-
5	5 + 5 (24 h)	40	593	inc.	-
6	20	40	162	2a	97:3
7	10	60	428	inc.	-
8	5 + 5 (24 h)	60	593	inc.	-
9	20	60	39	2a	97:3
10	10	80	39	2a	82:18
11	5 + 5 (24 h)	80	39	2a	66:34
12	20	80	39	2a/3a (81:19)	-

[a] incomplete

Wth enantioselective ratios over 90%, studies turned to exploring the substrate scope with the optimal reaction conditions. Two modifications were explored: Alternative ester derivatives and substituted aryl triflates. The ester derivatives were synthesized from the benzoic acid Birch reaction product (Table 1, entry 9), as illustrated in Scheme 2. Substituted aryl triflates were synthesized through the use of appropriately substituted 2-OTf-benzyl halide alkylating agents. These alkylating agents were synthesized in three steps from substituted salicylaldehydes (see SI).

Scheme 2. Esterification reactions.

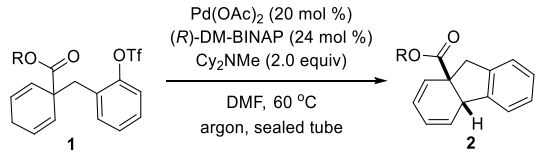


1i

1j R = Me, X = I, 61% yield
1k R = Allyl, X = Br, 34% yield
1l R = Bn, X = Br, 56% yield

Table 4 shows success with a range of ester derivatives. Methyl, ethyl, *t*-butyl and benzyl all work efficiently. The ethyl derivative was run at 1 mmol scale and provided an even higher yield than the smaller scale exploratory reactions. Allyl and carboxylic acid derivatives (entries 6 and 7) both decomposed to diphenyl side product; presumably the result of decarboxylative oxidation of the cyclohexandiene-carboxylate core.

Table 4. Ester derivative Heck reactions.



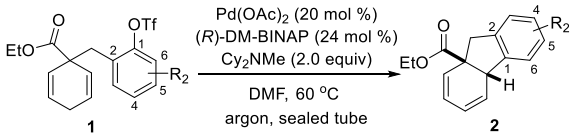
1 2

entry	R	time (h)	yield (%)	er	compd
1	Me, 1j	15	76	98:2	2j
2[a]	Et, 1b	39	73	98:2	2a
3[b]	Et, 1b	39	86	97:3	2a
4	*t*-Bu, 1h	38	74	97:3	2h
5	Bn, 1l	44	72	97:3	2l
6	allyl, 1k	41	dec.[c]	-	-
7	OH, 1i	19	dec.	-	-

[a] 0.08 mmol scale; [b] 1.0 mmol scale; [c] decomposed

Substituted benzene rings also afforded high yields and enantioselectivities (Table 5) for methyl and chloro substitution. Electron-withdrawing (NO_2 and CF_3) and electron-donating (OMe) groups failed to react. Substitution adjacent to the triflate group created steric hindrance to the process that degraded the rate and enantioselectivity (entry 3).

Table 5. Substituted aryl group Heck reactions.



1 2

entry	R	time (h)	yield (%)	er	compd
1	4-Me, 1c	17	72	96:4	2c
2	5-Me, 1d	219	77	98:2	2d
3	6-Me, 1e	288	73	60:40	2e
4	4-Cl, 1f	86	75	96:4	2f

In conclusion, a new catalytic enantioselective desymmetrizing Heck reaction has been achieved, and in most cases, it affords high yields and enantioselectivities in the construction of tricyclic rings with an all-carbon quaternary stereocenter. Modifications at the quaternary center and the aryl triflate ring are permitted. The process uses a Birch reduction-alkylation reaction to efficiently construct the desymmetrization substrate and is the first example of such an application.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectroscopic data for all compounds including ^{1}H, ^{13}C and 2-D NMR spectra, GC-MS, and chiral HPLC as a pdf file. Full Heck reaction condition screening tables are also available.

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Notes

The authors declare no competing financial interest.

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