Highly Stereoselective Synthesis of 1,2-Disubstituted Indanes by Pd-Catalyzed Heck/Suzuki Sequence of Diarylmethyl Carbonates

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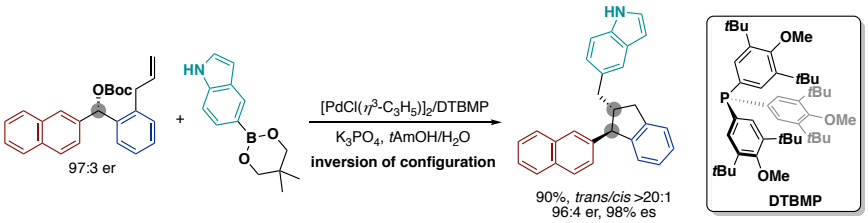
Supporting Information Placeholder



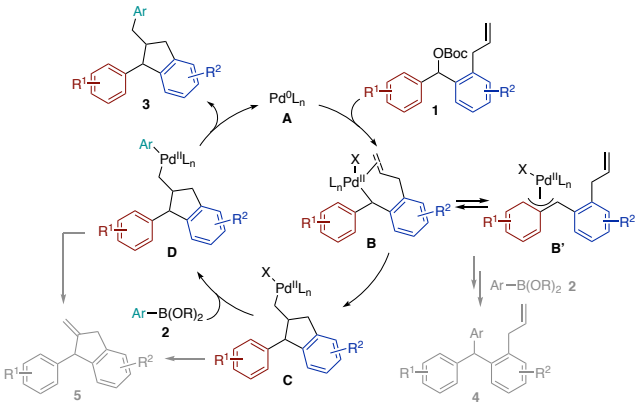
ABSTRACT: A palladium-catalyzed Mizoroki-Heck-type cyclization/Suzuki-Miyaura cross-coupling cascade of diarylmethyl carbonates with arylboronic acid derivatives has been developed to deliver the corresponding 1,2-disubstituted indanes in good yields with high diastereoselectivity (*trans/cis* >20:1). The key to achieve the high chemoselectivity and stereoselectivity is the use of the tris[3,5-di(*tert*-butyl)-4-methoxyphenyl]phosphine (DTBMP) ligand of remote steric hindrance. Moreover, the asymmetric synthesis is possible by the enantiospecific, stereoinvertive reaction of the optically active starting substrates to form the chiral indanes with high stereochemical fidelity (>98% es).

The Mizoroki-Heck-type reaction is one of the most powerful and reliable catalytic carbon-carbon bond forming reactions in modern organic synthetic chemistry.[1] In particular, the intramolecular versions (Mizoroki-Heck cyclization) are often applied to the construction of unique ring structures. Among them, the Mizoroki-Heck cyclization/cross-coupling sequence can readily provide multiply substituted cyclic frameworks, which are of prevalence in bioactive molecules and natural products. To date, synthetic chemists have developed various protocols for the palladium-catalyzed domino cyclization/cross-coupling of sp^2 C-hybridized aryl halides bearing the tethered alkene moiety with external nucleophiles to form versatile ring systems, which often includes the asymmetric synthesis.[2] On the other hand, the use of sp^3 C-hybridized alkyl electrophiles in such sequential transformations still remains underdeveloped while the simple Mizoroki-Heck-type reaction of alkyl halides is known to be promoted by several transition metal catalysts.[3] As a limited successful example, Oshima, Yorimitsu, and co-workers reported the cobalt-catalyzed tandem Mizoroki-Heck-type cyclization/cross-coupling of alkyl halides to afford the highly substituted five-membered cyclic systems.[4] However, the highly reactive Grignard reagents are necessary as the external carbon nucleophiles. Moreover, the cyclization event occurs *via* carbon-centered free radical species; therefore, the stereochemistry in the ring closure step is generally difficult to control. Thus, further development of such a cascade reaction, particularly, stereocontrolled process with the alkyl electrophiles is highly appealing.[5] Herein, we report a palladium-catalyzed highly diastereoselective Mizoroki-Heck cyclization/Suzuki-Miyaura coupling sequence of diarylmethyl carbonates with arylboronic acid derivatives to furnish the corresponding 1,2-disubstituted indanes with high *trans*-selectivity (*trans/cis* >20:1). Furthermore, the asymmetric synthesis is also possible by the enantiospecific, stereoinvertive cascade reaction of the readily available optically active starting substrates with high stereochemical fidelity (>98% es). The related nickel-catalyzed enantiospecific Mizoroki-Heck-type cyclization of secondary benzyl ethers was developed by Jarvo, but application to the sequential bond-forming process is still a formidable challenge.[6]

We have recently developed the palladium-catalyzed intramolecular Mizoroki-Heck-type reaction of diarylmethyl *tert*-butyl carbonates.[7] In our continuing interest in this chemistry, we envisioned our blueprint for the sequential coupling in conjunction with the arylboronic acid external nucleophiles. Our working hypothesis is illustrated in Scheme 1. The initial oxidative addition of diarylmethyl *tert*-butyl carbonate **1** to Pd^0L_n **A** forms the corresponding σ-benzylpalladium **B**, which is in equilibrium with the π-benzylpalladium **B'**.[8] The subsequent migratory insertion of the pendant alkene moiety affords the alkylpalladium intermediate **C**. The interception with the arylboronic acid **2** (transmetalation; **C** to **D**) followed by the reductive elimination furnishes the targeted 1,2-disubstituted indane **3** and the starting Pd^0L_n **A** to complete the catalytic cycle.

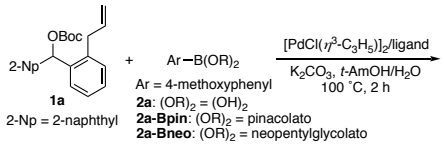
However, there are several challenges associated with the aforementioned reaction design. First one is the chemoselectivity issue: the benzylpalladium **B** or **B'** could directly undergo the Suzuki-Miyaura cross-coupling reaction with the boronic acid **2** through transmetalation and reductive elimination to deliver the undesired triarylmethane **4**.[9] Similarly, the alkylpalladiums **C** and **D** are prone to β-hydride elimination, giving the simple Mizoroki-Heck-type cyclization byproduct **5**.[10] Second is the control of relative stereochemistry (*trans* or *cis*) of the adjacent chiral carbon centers in the insertion step (**B** to **C**). Finally, the configuration at the point chirality of the starting diarylmethyl carbonate **1** (inversion, retention, or racemization) should be mentioned when the optically active substrate is employed.

Scheme 1. Working Hypothesis of Pd-Catalyzed Mizoroki-Heck Cyclization/Suzuki-Miyaura Sequence and Conceivable Challenges



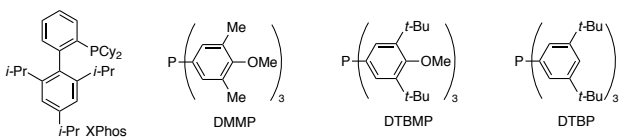
On the basis of the above scenario, we began optimization studies with the diarylmethyl *tert*-butyl carbonate **1a**, 4-methoxyphenylboronic acid (**2a**), [PdCl(η^3-C_3H_5)]$_2$ catalyst, K_2CO_3 base, and *t*-AmOH (2-methyl-2-butanol)/H_2O mixed solvent system to identify the appropriate ligand (Table 1). An initial attempt with the XPhos ligand, which was the optimal ligand in our previous work,[7] resulted in the formation of the desired **3aa** albeit with moderate yield (48%), *trans*/*cis* selectivity (1:1.2), and chemoselectivity (**4aa**, 13%; **5a**, 31%; entry 1). To suppress the β-hydride elimination en route to **5a**, we next investigated some electron-rich, bulky alkylphosphine ligands (entries 2–5).[11] Although the yield of **3aa** increased, a significant amount of the Mizoroki-Heck-type product **5a** was still formed. On the other hand, unexpectedly, the simple PPh_3 also promoted the reaction to afford **3aa** in 82% yield (entry 6). Inspired by this intriguing outcome, we moved our attention to triarylphosphine ligands. Whereas the electron-withdrawing ligand was ineffective (entry 7), electron-donating P(4-$MeOC_6H_4$)$_3$, DMMP, and DTBMP produced **3aa**, particularly with DTBMP chemoselectively providing **3aa** with high *trans/cis* selectivity (13:1; entry 10). The control experiment with the DTBP ligand maintained the high chemoselectivity but lowered the stereoselectivity (entry 11), thus suggesting that the *t*Bu groups at the meta positions mainly suppress the β-hydride elimination and both *t*Bu and MeO groups affect the stereoselectivity in the insertion step (**B** to **C** in Scheme 1).[12] Subsequent fine-tuning finally revealed that the reaction of **1a** proceeded more efficiently and stereoselectively with the corresponding neopentylglycol ester **2a-Bneo** and K_3PO_4 base to afford **3aa** in 94% isolated yield with >20:1 *trans/cis* selectivity (entry 14). Some additional observations are to be noted: bidentate ligands generally produced a mixture of **3aa**, **4aa**, and **5a**; other Pd sources such as $Pd(OAc)_2$, $PdCl_2$, and $Pd_2(dba)_3$ totally shut down the reaction; the external base was not necessary but increased the product yield (see the Supporting Information for more detailed optimization studies).

Table 1. Optimization Studies for Pd-Catalyzed Mizoroki-Heck/Suzuki-Miyaura Sequence of Diarylmethyl Carbonate 1a with Arylboronic acid 2a[a]



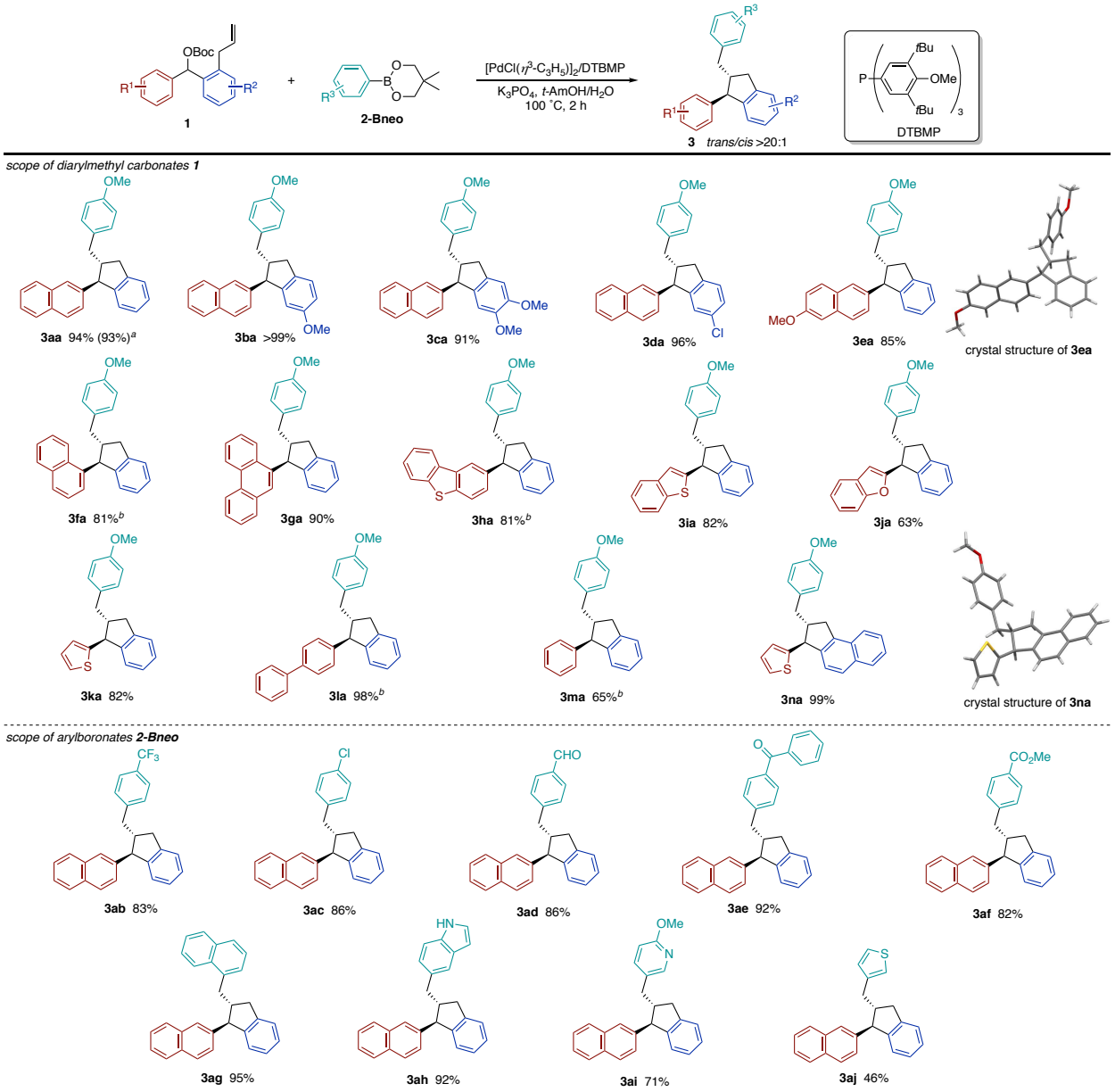
entry	**2**	ligand	yield (%)[b]		
			3aa, *trans/cis*[c]	**4aa**	**5a**
1	**2a**	XPhos	48, 1:1.2	13	31
2	**2a**	P(*t*-Bu)$_3$	0, –	0	15
3	**2a**	PCy_3	52, 1:1.8	0	40
4	**2a**	PCy_2Ph	74, 1.6:1	0	16
5	**2a**	$PCyPh_2$	79, 1:1.3	0	19
6	**2a**	PPh_3	82, 1:1.3	7	10
7	**2a**	P(4-$CF_3C_6H_4$)	0, –	39	0
8	**2a**	P(4-$MeOC_6H_4$)	69, 2.6:1	0	30
9	**2a**	DMMP	80, 2.8:1	0	15
10	**2a**	DTBMP	83, 13:1	0	0
11	**2a**	DTBP	81, 4.6:1	0	6
12	**2a-Bpin**	DTBMP	82, >20:1	0	3
13	**2a-Bneo**	DTBMP	79, >20:1	0	0
14[d]	**2a-Bneo**	DTBMP	(94), >20:1	0	2

[a] Conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), [PdCl(η^3-C_3H_5)]$_2$ (0.0050 mmol), ligand (0.022 mmol), K_2CO_3 (0.60 mmol), *t*-AmOH/H_2O (2.0/0.1 mL), 100 °C, 2 h, N_2. [b] Estimated by ^{1}H NMR with 1-methylnaphthalene as the internal standard. Isolated yield is in parentheses. [c] Determined by ^{1}H NMR of crude material. [d] With **2a-Bneo** (0.21 mmol) and K_3PO_4 (0.20 mmol).



With the optimal conditions in hand (Table 1, entry 14), we first examined the scope of the diarylmethyl carbonates **1** (Scheme 2). Both electron-donating and -withdrawing groups on the benzene ring were well tolerated

Scheme 2. Products of Pd-Catalyzed Mizoroki-Heck Cyclization/Suzuki-Miyaura Coupling Sequence of Various Diarylmethyl Carbonates 1 and Arylboronates 2-Bneo.[c]



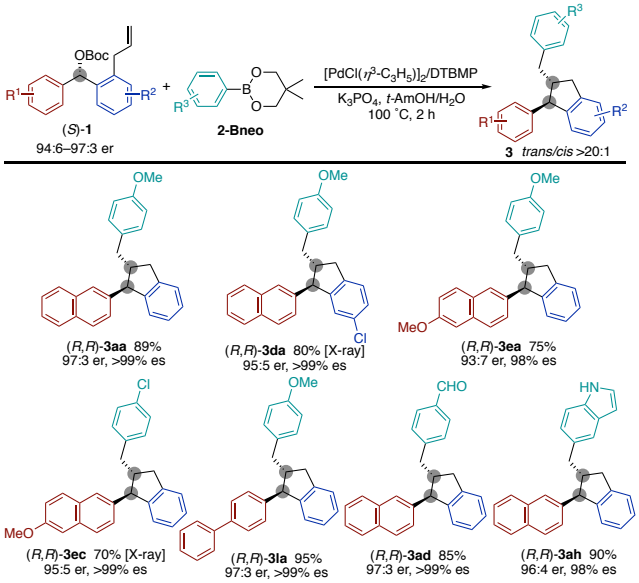
[a] On a 1.0 mmol scale with 1.01 equiv of **2a-Bneo**. [b] For 16 h. [c]Conditions: **1** (0.20 mmol), **2-Bneo** (0.21 mmol), [PdCl(η^3-C_3H_5)]$_2$ (0.0050 mmol), DTBMP (0.022 mmol), K_3PO_4 (0.20 mmol), *t*AmOH/H_2O (2.0/0.1 mL), 100 ˚C, 2 h, N_2.

to form the corresponding substituted indanes **3ba**–**3da** in high yields (91–>99%). The 2-naphthalene substituent could also be replaced with methoxy-substituted naphthalene, 1-naphthalene, and higher fused phenanthrene moieties (**3ea**–**3ga**; 81–90%). Additionally, the heteroaromatic substrates such as dibenzothiophene, benzothiophene, and benzofuran could also be employed (**3ha**–**3ja**; 63–82%). Particularly notable is the successful transformation of conceivably more challenging monocyclic substrates:[13] thiophene-substituted, biphenyl-substituted, and even simple phenyl-substituted diarylmethyl carbonates smoothly underwent the reaction to deliver the corresponding 1,2-disubstituted indanes **3ka**–**3ma** in acceptable yields. In addition to the indane structure, the cyclopentanaphthalene framework **3na** could also be readily prepared with high chemo- and stereoselectivity. The scope of arylboronates **2-Bneo** is also substantially broad. The arylboronates bearing electron-withdrawing trifluoromethyl and chloro groups were amenable without any difficulty (**3ab** and **3ac**). The carbonyl functions including aldehyde, ketone, and ester were equally compatible under the standard reaction conditions (**3ad**–**3af**). The sterically demanding 1-naphthylboronate was also reactive to afford **3ag** in a high yield. Furthermore, a range of heteroarylboronates was successfully coupled with **1a**, and free NH-indole, pyridine, and thiophene substituents were thus readily introduced to the indane scaffold (**3ah**–**3aj**). In all cases, the high diastereoselectivity was observed (*trans/cis* >20:1). The *trans* stereochemistry of **3ea** and **3na** was unambiguously confirmed by X-

ray analysis (CCDC 1981987 and 1981988). The reaction was also scalable and easily conducted on a 1.0 mmol scale without any erosion of yield and stereoselectivity, thus indicating the good reproducibility and reliability (**3aa**).[14]

We finally focused on the enantiospecificity of the reaction (Scheme 3). Pleasingly, the readily prepared optically active (*S*)-**1a**[15] was converted with inversion of configuration to the enantioenriched (*R,R*)-**3aa** in high enantiospecificity (97:3 er, >99% es). The steric and electronic nature of diarylmethyl carbonates **1** (chloro, methoxy, and biphenyl substituents) and arylboronates **2** (methoxy, chloro, formyl, and NH-indolyl functions) did not affect the enantiospecificity, and the corresponding chiral 1,2-disubstituted indanes were obtained with high stereochemical fidelity (98 to >99% es). The absolute configurations of (*R,R*)-**3da** and (*R,R*)-**3ec** were determined by the single X-ray crystallographic analysis (CCDC 1984967 and 1984968), which suggests the S_N2-type oxidative addition with inversion of configuration (**A** to **B** in Scheme 1).[16]

Scheme 3. Optically Active Products by Enantiospecific, Stereoinvertive Pd-Catalyzed Mizoroki-Heck Cyclization/Suzuki-Miyaura Coupling Sequence of Chiral Diarylmethyl Carbonates (*S*)-1 and Arylboronates 2-Bneo.[a]



[a]% es = (% ee of product **3**/% ee of starting substrate **1**) x 100.

In conclusion, we have developed a Pd/DTBMP-catalyzed Mizoroki-Heck/Suzuki-Miyaura cascade of diarylmethyl carbonates with arylboronates. The reaction is compatible with a wide range of functional groups and proceeds chemoselectively and diastereoselectively to form the corresponding 1,2-disubstituted indanes with high *trans* selectivity. Additionally, the optically active indanes are also accessible by using the enantiospecific, stereoinvertive reaction of readily available chiral substrates with high stereochemical fidelity. The newly developed protocol can provide an avenue to chiral carbocyclic frameworks with multiple substituents, which are prevalent in natural products and bioactive molecules. Detailed investigations of the origin of uniquely high chemo- and stereoselectivity associated with DTBMP ligand[17] and further developments of related stereospecific and stereoselective palladium catalysis are now in progress.

ASSOCIATED CONTENT

Supporting Information

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

^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} NMR spectra, ORTEP drawing, detailed optimization studies (PDF)

Accession Codes

CCDC 1981987, 1981988, 1984967, and 1984968 contains 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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(14) Unfortunately, attempts to cyclize an alkene tethered to a monoaryl carbonate (NpCH(OBoc)$CH_2CH_2CH_2CH{=}CH_2$) were unsuccessful. See the Supporting Information for more substrate limitations.

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(17) Given the steric bulkiness of DTBMP, one possibility is the formation of a low-coordinating Pd species. Actually, the reaction with a Pd/ligand 1:1 ratio increased the *trans* stereoselectivity of **3aa** while the direct Suzuki-Miyaura coupling byproduct **4aa** was still competitive (see the Supporting Information for more details). For the related work on formation of the low-coordinating metal species with *meta*-substituted phosphine ligands and their uniquely high catalytic activity, see: (a) Niyomura, O.; Tokunaga, M.; Obora, Y.; Iwasawa, T.; Tsuji, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 1287. (b) Ohta, H.; Tokunaga, M.; Obora, Y.; Iwai, T.; Iwasawa, T.; Fujihara, T.; Tsuji, Y. *Org. Lett.* **2007**, *9*, 89. (c) Fujihara, T.; Semba, K.; Terao, J.; Tsuji, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 1472.