JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

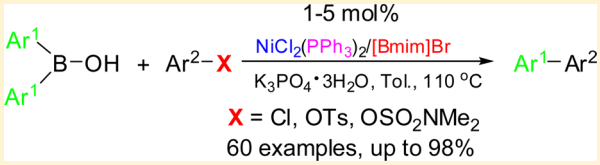
N-Heterocyclic Carbene-Assisted, Bis(phosphine)nickel-Catalyzed Cross-Couplings of Diarylborinic Acids with Aryl Chlorides, Tosylates, and Sulfamates

Haihua Ke, Xiaofeng Chen, and Gang Zou*

Department of Fine Chemicals, East China University of Science & Technology, 130 Meilong Road, Shanghai 200237, China

Supporting Information

ABSTRACT: Efficient bis(phosphine)nickel-catalyzed cross-couplings of diarylborinic acids with aryl chlorides, tosylates, and sulfamates have been effected with an assistance of N-heterocyclic carbene (NHC) generated in situ from *N*,*N*′-dialkylimidazoliums, e.g., *N*-butyl-*N*′-methylimidazolium bromide ([Bmim]Br), in toluene using $K_3PO_4 \cdot 3H_2O$ as base. In contrast to bis(NHC)nickel-catalyzed conventional Suzuki coupling of arylboronic acids, mono(NHC)bis(phosphine)nickel species generated in situ from $Ni(PPh_3)_2Cl_2$/[Bmim]Br displayed high catalytic activities in the cross-couplings of diarylborinic acids. The structural influences from diarylborinic acids were found to be rather small, while electronic factors from aryl chlorides, tosylates, and sulfamates affected the couplings remarkably. The couplings of electronically activated aryl chlorides, tosylates, and sulfamates could be efficiently effected with 1.5 mol % $NiCl_2(PPh_3)_2$/[Bmim]Br as catalyst precursor to give the biaryl products in excellent yields, while 3−5 mol % loadings had to be used for the couplings of non- and deactivated ones. A small *ortho*-substitutent on the aromatic ring of aryl chlorides, tosylates, and sulfamates was tolerable. Applicability of the nickel-catalyzed cross-couplings in practical synthesis of fine chemicals has been demonstrated in process development for a third-generation topical retinoid, Adapalene.



INTRODUCTION

Chemistry of palladium-catalyzed Suzuki coupling of arylboronic acids has been well-established.[1] However, its applications in large scale production are still hampered by the costs of palladium catalysts and/or expensive substrates, especially arylboronic acids. Developments of efficient nickel catalysts pioneered by Percec[2] and Fu[3] et al. have promised great potentials not only in reducing the catalyst costs but also in taking advantage of electrophiles that are challengeable to palladium-catalyzed Suzuki coupling, such as a variety of phenol derivatives and alkyl halides.[2−4] Comparably, it is still undeveloped to use high-order arylborons ($Ar_2B(OH)$, Ar_3B and $[Ar_4B]M$) in Suzuki coupling, although they not only have higher atom economies but also could be more economically prepared than the corresponding arylboronic acids.[5] We recently have effected cross-couplings of diarylborinic acids ($Ar_2B(OH)$) with aryl (pseudo)halides by using a phosphine/nickel catalyst system ($NiCl_2(PAr_3)_2/2PAr_3$) in developing cost-effective Suzuki coupling.[6] However, similar to most phosphine/nickel catalyst systems for Suzuki coupling, four or more equivalents of phosphine ligand relative to nickel had to be used to maintain an acceptable catalytic efficiency because of dissociation and decomposition of phosphines. N-Heterocyclic carbenes (NHCs) have been well-known to be better supporting ligands than phosphines for robust transition metal complexes.[7] In fact, mono(NHC)palladium complexes of sterically demanding N-heterocyclic carbenes, e.g., 1,3-di[2,6-(diisopropyl)phenyl]-imidazolylidene (IPr) etc., have been elegantly established by Nolan,[8] Organ[9] and Glorius[10] et al. to be the most efficient catalysts for Suzuki coupling of aryl chlorides, while bis(NHC) palladium species seemed too stable to be active. In sharp contrast, bis(NHC)nickel species have appeared to be more catalytically active than the mono(NHC)nickel ones in Suzuki coupling, although the NHC/nickel catalyst systems are still far away from being established.[4,11−17] For example, bis(NHC) nickel species had been identified by in situ NMR and EXAFS and proposed to be true catalysts in a nickel ion-containing ionic liquid, bis(*N*-butyl-*N*′-methylimidazolium)tetrachloronickelate ($[Bmim]_2NiCl_4$), catalyzed Suzuki coupling.[12] Radius et al. even reported selective Suzuki coupling of perfluorinated arenes by using a bis(NHC)nickel complex of 1,3-di(isopropyl)imidazol-2-ylidene, $[Ni_2(di^iPrim)_4(COD)]$.[13a] Nickel complexes (**I**−**IV**) supported by bridged chelating bis(NHC) ligands had been further designed and used as catalyst precursors in Suzuki coupling, which showed good catalytic efficiencies if in the presence of 2−5 equiv of phosphine coligand (Figure 1).[17]

As a part of our ongoing efforts to develop practical arylation methods using diarylborinic acids, we report herein efficient cross-couplings of diarylborinic acids with aryl chlorides, tosylates, and sulfamates catalyzed by mono(NHC), bis(phosphine) coligated nickel catalysts generated in situ from bis(phosphine)nickel chloride and *N*,*N*′-dialkylimidazoliums, such as [Bmim]Br or [diBim]Br, etc., and its application in practical synthesis of a third-generation topical retinoid, Adapalene.

Received: June 10, 2014
Published: July 15, 2014

dx.doi.org/10.1021/jo501291y | J. Org. Chem. 2014, 79, 7132−7140

RESULTS AND DISCUSSION

Cross-Coupling of Aryl Chlorides. Cross-coupling of bis(*p*-tolyl)borinic acid (**1a**) with electronically deactivated aryl chloride, 4-(benzyloxy)phenyl chloride (**2a**), was chosen as model reaction to evaluate NHC/Ni catalyst systems since the reaction has been recently effected in our laboratory by using $Pd/(POR)_3/IPr$[5d] and $NiCl_2(PAr_3)_2/2PAr_3$[6a] catalyst systems. No reaction was observed with the $[Bmim]_2NiCl_4$ catalyst system reported for Suzuki coupling of arylboronic acids with aryl chlorides under otherwise identical conditions.[12] Considering bis(NHC)nickel complexes, e.g., $NiCl_2(NHC)_2$, had been identified in the $[Bmim]_2NiCl_4$ catalyst system, a combination of $NiCl_2$ with 2 equiv of [Bmim]Br in the presence of $K_3PO_4 \cdot 3H_2O$, which was heated prior to addition of substrates to in situ generate NHC nickel species, was tested subsequently. The reaction did occur with 3 mol % $NiCl_2$ and 6 mol % [Bmim]Br, but sluggishly even in the presence of 6 mol % PPh_3 as coligand for nickel (Table 1, entries 1 and 2). However, when the reaction was run in toluene, the yield of **3aa** remarkably increased to 77%. The preformation of catalytically active nickel species proved crucial for the model reaction to take place efficiently since **3aa** was isolated in only 10% yield when all components of the catalyst system and substrates were added simultaneously (Table 1, entries 3 and 4). When $NiCl_2(PPh_3)_2$ was used in placement of $NiCl_2$ and PPh_3, it was not necessary any more to preform the catalytic species (Table 1, entry 5). An increase in the mole ratios of [Bmim]Br to $NiCl_2(PPh_3)_2$, thus NHC to Ni, from 2/1 to 3/1 and 4/1 decreased the yields of product **3aa** significantly from 78 to 64 and 43%, respectively. In contrast, use of 3 mol % $NiCl_2(PPh_3)_2$ with 3 mol % [Bmim]Br, namely equivalent NHC to Ni, gave an excellent yield (93%) for **3aa** under otherwise identical conditions (Table 1, entry 8). These results implied that some mono(NHC), bis(phosphine) coligated nickel species generated in situ, e.g., $Ni(PPh_3)_2(NHC)$, should be more catalytically active in the cross-coupling of diarylborinic acids with aryl chlorides although bis(NHC)nickel complexes have been generally used as catalytic precursors or even proposed to be the active species in NHC/nickel catalyst systems for the conventional Suzuki coupling of arylboronic acids. The yield of **3aa** failed to further increase upon increasing the catalyst loading to 4 mol % while a lower yield (56%) was obtained with 2 mol % $NiCl_2(PPh_3)_2$/[Bmim]Br (Table 1, entries 9 and 10).

The control experiments in the absence of a phosphine or NHC precursor indicated that phosphines should be more important than NHCs in the NHC/phosphine coligated nickel catalysts although NHCs have generally played a major role in transition metal catalysts mixed-ligated by NHC and other ligands (Table 1, entries 11−13).[9,18−20] Screening of phosphine ligands showed that the electron-rich triarylphosphine P(4-MeOPh)$_3$ performed comparably to PPh_3 while tricyclohexylphosphine (PCy_3) showed almost no activity in the

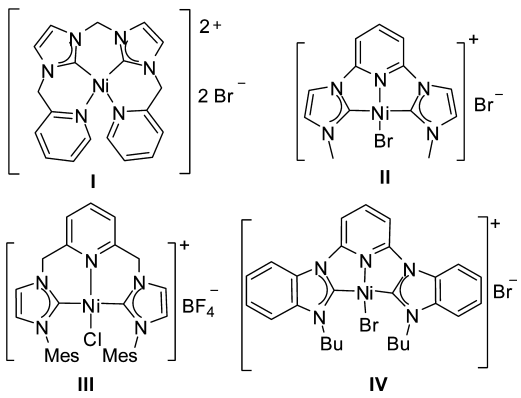
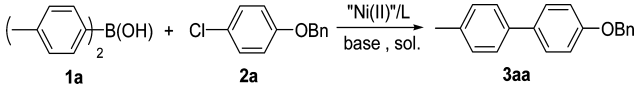


Figure 1. Selected bis(NHC)nickel catalyst precursors in Suzuki coupling.

Table 1. Optimization of the Nickel-Catalyzed Cross-Coupling of Diarylborinic Acid with Aryl Chloride[a]



1a 2a 3aa

entry	Ni(II) (mol %)	L (mol %)	base	solvent	yield (%)[b]
1[c]	$NiCl_2$ (3)	[Bmim]Br (6)	$K_3PO_4 \cdot 3H_2O$	dioxane	12
2[c]	$NiCl_2$ (3)/PPh_3 (6)	[Bmim]Br (6)	$K_3PO_4 \cdot 3H_2O$	dioxane	35
3[c]	$NiCl_2$ (3)/PPh_3 (6)	[Bmim]Br (6)	$K_3PO_4 \cdot 3H_2O$	toluene	77
4	$NiCl_2$ (3)/PPh_3 (6)	[Bmim]Br (6)	$K_3PO_4 \cdot 3H_2O$	toluene	10
5	$NiCl_2(PPh_3)_2$ (3)	[Bmim]Br (6)	$K_3PO_4 \cdot 3H_2O$	toluene	78
6	$NiCl_2(PPh_3)_2$ (3)	[Bmim]Br (9)	$K_3PO_4 \cdot 3H_2O$	toluene	64
7	$NiCl_2(PPh_3)_2$ (3)	[Bmim]Br (12)	$K_3PO_4 \cdot 3H_2O$	toluene	43
8	$NiCl_2(PPh_3)_2$ (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	93
9	$NiCl_2(PPh_3)_2$ (4)	[Bmim]Br (4)	$K_3PO_4 \cdot 3H_2O$	toluene	94
10	$NiCl_2(PPh_3)_2$ (2)	[Bmim]Br (2)	$K_3PO_4 \cdot 3H_2O$	toluene	56
11	$NiCl_2$ (3)	[Bmim]Br (6)	$K_3PO_4 \cdot 3H_2O$	toluene	trace
12	$NiCl_2(PPh_3)_2$ (3)	–	$K_3PO_4 \cdot 3H_2O$	toluene	48
13	$NiCl_2(PPh_3)_2$ (3)	TBAB (3)	$K_3PO_4 \cdot 3H_2O$	toluene	55
14	$NiCl_2$[P(4-MeOPh)$_3$]$_2$ (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	91
15	$NiCl_2(PCy_3)_2$ (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	8
16	$NiCl_2$(dppm) (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	20
17	$NiCl_2$(dppe) (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	24
18	$NiCl_2$(dppp) (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	23
19	$NiCl_2$(dppb) (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	69
20	$NiCl_2$(dppf) (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	84
21	$NiCl_2(PPh_3)_2$ (3)	[^{t}Bumim]I (3)	$K_3PO_4 \cdot 3H_2O$	toluene	78
22	$NiCl_2(PPh_3)_2$ (3)	[Emim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	82
23	$NiCl_2(PPh_3)_2$ (3)	[Pmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	87
24	$NiCl_2(PPh_3)_2$ (3)	[Hmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	81
25	$NiCl_2(PPh_3)_2$ (3)	[diBim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	90
26	$NiCl_2(PPh_3)_2$ (3)	[di^{t}Buim]Cl (3)	$K_3PO_4 \cdot 3H_2O$	toluene	75
27	$NiCl_2(PPh_3)_2$ (3)	[diEim]Br (3)	$K_3PO_4 \cdot 3H_2O$	toluene	83
28	$NiCl_2(PPh_3)_2$ (3)	[diMim]I (3)	$K_3PO_4 \cdot 3H_2O$	toluene	80
29	$NiCl_2(PPh_3)_2$ (3)	[Phmim]I (3)	$K_3PO_4 \cdot 3H_2O$	toluene	71
30	$NiCl_2(PPh_3)_2$ (3)	IPr·HCl (3)	$K_3PO_4 \cdot 3H_2O$	toluene	59
31	$NiCl_2(PPh_3)_2$ (3)	IMes·HCl (3)	$K_3PO_4 \cdot 3H_2O$	toluene	56
32	$NiCl_2(PPh_3)_2$ (3)	IPh·HCl (3)	$K_3PO_4 \cdot 3H_2O$	toluene	66
33	$NiCl_2(PPh_3)_2$ (3)	[Mesmim]I (3)	$K_3PO_4 \cdot 3H_2O$	toluene	44
34	$NiCl_2(PPh_3)_2$ (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	dioxane	34
35	$NiCl_2(PPh_3)_2$ (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	THF	64
36	$NiCl_2(PPh_3)_2$ (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	CH_3CN	42
37	$NiCl_2(PPh_3)_2$ (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	DMF	69
38	$NiCl_2(PPh_3)_2$ (3)	[Bmim]Br (3)	$K_3PO_4 \cdot 3H_2O$	EtOH	11
39	$NiCl_2(PPh_3)_2$ (3)	[Bmim]Br (3)	K_2CO_3	toluene	30
40	$NiCl_2(PPh_3)_2$ (3)	[Bmim]Br (3)	Na_2CO_3	toluene	19
41	$NiCl_2(PPh_3)_2$ (3)	[Bmim]Br (3)	NaOH	toluene	58

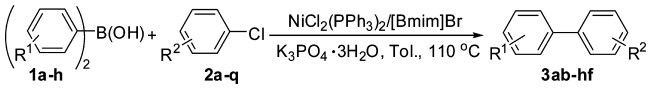
[a]Reaction conditions: **1a** (1.3 mmol), **2a** (2 mmol), base (5.2 mmol), solvent (5 mL), N_2, 10 h, reflux. [b]Isolated yields. [c]Preformation of Ni/NHC/PPh_3 complex before addition of substrates.

dx.doi.org/10.1021/jo501291y | J. Org. Chem. 2014, 79, 7132−7140

$NiCl_2(PR_3)_2$/imidazolium catalyst system. Among the common bidentate phosphines tested, only 1,1′-bis(diphenylphosphino)-ferrocene (dppf) showed an acceptable performance, but still poorer than those of PPh_3 and P(4-MeOPh)$_3$. The structure of imidazoliums also remarkably affected the activities of the $NiCl_2(PPh_3)_2$/imidazolium catalyst system. Use of either more or less sterically demanding dialkylimidazoliums, such as *N*-*tert*-butyl-*N*′-methylimidazolium iodide ([^{t}Bumim]I) and *N*,*N*′-di(*tert*-butyl)imidazolium chloride ([di^{t}Buim]Cl), or *N*-ethyl-*N*′-methylimidazolium bromide ([Emim]Br) and *N*,*N*′-di(methyl)imidazolium iodide ([diMim]I) in the $NiCl_2(PPh_3)_2$/imidazolium system led to slightly lower yields (75−82%) for **3aa**, while *N*,*N*′-di(butyl)imidazolium bromide ([diBim]Br) gave a comparable yield (90%) to that (93%) of [Bmim]Br (Table 1, entries 21−28). *N*-Aryl imidazoliums, such as *N*-Ph, mesityl, or 2,6-diisopropylphenyl ones, displayed poor performances in the $NiCl_2(PPh_3)_2$/imidazolium system (Table 1, entries 29−33). The other common solvents (THF, DMF, CH_3CN, EtOH and dioxane) and bases (K_2CO_3, Na_2CO_3 and NaOH) provided **3aa** in lower yields (11−69%) than the combination of toluene with $K_3PO_4{\cdot}3H_2O$ for the model reaction. Finally, an optimal catalyst system and reaction conditions were set as $NiCl_2(PPh_3)_2$/[Bmim]Br in toluene using $K_3PO_4{\cdot}3H_2O$ as base, under which scope of the mono(NHC)bis(phosphine)nickel-catalyzed cross-coupling of aryl chlorides with diarylborinic acids was explored (Table 2).

Similar to the model reaction, electron-neutral or -rich aryl chlorides reacted with **1a** to give products **3ab**, **3ae** and **3ah** in 92−98% yields with 3 mol % catalyst loading (Table 2, entries 1, 4 and 7). Aryl chlorides activated by an electron-withdrawing group, e.g., CHO, CN, CO_2Me and $COCH_3$, at *para*- or *meta*-position of aromatic ring were more reactive and excellent yields could be obtained for the corresponding coupling products **3ak**, **3al**, **3ao**, **3ap**, and **3aq** even with a lower (1.5 mol %) catalyst loading in shorter reaction time (Table 2, entries 10, 11 and 15−17). A small *ortho*-substituent on the aromatic ring of aryl chlorides was tolerable although a large one significantly hampered their couplings with diarylborinic acids. For example, aryl chlorides bearing an *ortho*-methyl (**2c**), -methoxy (**2f**) or -cyano (**2m**) substituent could be effectively coupled to give the corresponding products **3ac** (95%), **3af** (93%) or **3am** (97%) in high yields (Table 2, entries 2, 5 and 12) while the ones bearing 2,6-dimethyl groups (**2d**), an *ortho*-isopropoxy (**2g**) or -acetyl (**2n**) group afforded the products **3ad** (33%), **3ag** (63%) or **3an** (45%) in significantly lower yields (Table 2, entries 3, 6 and 13). For 2-chloroacetophenone (**2n**), 3 mol % catalyst loading could afford a satisfactory yield (94%) for **3an** (Table 2, entries 13 and 14).[21] Aryl chlorides with a free amino group appeared to be tolerable although the yields slightly decreased for both 4-chloroaniline (**2i**, 83%) and its *ortho*-isomer (**2j**, 79%) (Table 2, entries 8 and 9). Investigation of structural effects of diarylborinic acids on the NHC assisted, $NiCl_2(PPh_3)_2$-catalyzed cross-coupling reaction showed that influences of both electronic and steric factors were negligible. For example, the cross-couplings of 4-(benzyloxy)phenyl chloride (**2a**) with diarylborinic acids with an electron-withdrawing (4-F, **1d**) or -donating (4-OMe, **1c**; 2-Me, **1e**; 2-Et, **1f**; 2-OMe, **1g**; and 2-O^{i}Pr, **1h**) substituent at either *para*- or *ortho*-position of aromatic rings afforded the corresponding biaryls **3ca**−**3ha** in good to excellent yields (Table 2, entries 19−24). However, an accumulative effect of steric hindrance of diarylborinic acids and aryl chlorides was observed for the reactions of

Table 2. Scope of the Cross-Coupling of Diarylborinic Acids with Aryl Chlorides[a]



1a-h 2a-q 3ab-hf

entry	R^1 (1)	R^2 (2)	cat (mol %)	*t* (h)	yield (%)[b]
1	4-Me (**1a**)	4-Me (**2b**)	3	10	98 (**3ab**)
2	4-Me (**1a**)	2-Me (**2c**)	3	10	95 (**3ac**)
3	4-Me (**1a**)	2,6-diMe (**2d**)	3	10	33 (**3ad**)
4	4-Me (**1a**)	4-OMe (**2e**)	3	10	96 (**3ae**)
5	4-Me (**1a**)	2-OMe (**2f**)	3	10	93 (**3af**)
6	4-Me (**1a**)	2-O^{i}Pr (**2g**)	3	10	63 (**3ag**)
7	4-Me (**1a**)	4-NMe_2 (**2h**)	3	10	92 (**3ah**)
8	4-Me (**1a**)	4-NH_2 (**2i**)	3	10	83 (**3ai**)
9	4-Me (**1a**)	2-NH_2 (**2j**)	3	10	79 (**3aj**)
10	4-Me (**1a**)	4-CN (**2k**)	1.5	6	95 (**3ak**)
11	4-Me (**1a**)	3-CN (**2l**)	1.5	6	93 (**3al**)
12	4-Me (**1a**)	2-CN (**2m**)	1.5	6	97 (**3am**)
13	4-Me (**1a**)	2-Ac (**2n**)	1.5	10	45 (**3an**)
14	4-Me (**1a**)	2-Ac (**2n**)	3	10	94 (**3an**)
15	4-Me (**1a**)	4-Ac (**2o**)	1.5	6	98 (**3ao**)
16	4-Me (**1a**)	4-CO_2Me (**2p**)	1.5	7	96 (**3ap**)
17	4-Me (**1a**)	4-CHO (**2q**)	1.5	8	95 (**3aq**)
18[c]	H (**1b**)	4-OBn (**2a**)	3	10	94 (**3ba**)
19	4-OMe (**1c**)	4-OBn (**2a**)	3	10	90 (**3ca**)
20	4-F (**1d**)	4-OBn (**2a**)	3	10	88 (**3da**)
21	2-Me (**1e**)	4-OBn (**2a**)	3	10	90 (**3ea**)
22	2-Et (**1f**)	4-OBn (**2a**)	3	10	84 (**3fa**)
23	2-OMe (**1g**)	4-OBn (**2a**)	3	10	88 (**3ga**)
24	2-O^{i}Pr (**1h**)	4-OBn (**2a**)	3	10	89 (**3ha**)
25	2-Me (**1e**)	2-OMe (**2f**)	3	10	72 (**3ef**)
26	2-Et (**1f**)	2-OMe (**2f**)	3	10	54 (**3ff**)
27	2-OMe (**1g**)	2-OMe (**2f**)	3	10	71 (**3gf**)
28	2-O^{i}Pr (**1h**)	2-OMe (**2f**)	3	10	65 (**3hf**)

[a]Reaction conditions: **1** (1.3 mmol), **2** (2 mmol), $K_3PO_4{\cdot}3H_2O$ (5.2 mmol), toluene (5 mL), N_2, 10 h. [b]Isolated yield. [c]0.65 mmol of diphenylborinic anhydride was used.

2-methoxyphenyl chloride (**2f**) with *ortho*-substituted diarylborinic acids **1e**−**1h**, affording **3ef**−**3hf** in just modest yields (Table 2, entries 25−28).

Cross-Couplings of Aryl Tosylates and Sulfamates. Phenols are the most abundant naturally occurring aryl sources.[22] Therefore, it is important to take advantage of readily available phenol derivatives, such as tosylates and sulfamates, as the electrophile counterparts in transition metal-catalyzed cross-couplings.[2,4,23] Using the established catalyst system, $NiCl_2(PPh_3)_2$/[Bmim]Br, for cross-coupling of aryl chlorides with diarylborinic acids, reaction of aryl tosylates was investigated at first considering their ready availability at low cost and easy to handle properties (Table 3). A lower reactivity but with a larger electronic effect was observed from aryl tosylates than that from aryl chlorides in their cross-couplings with diarylborinic acids. For example, reaction of 4-methoxyphenyl tosylate (**4a**) with bis(*p*-tolyl)borinic acid (**1a**) gave biaryl **3ae** in only 47 and 68% yields with 3 and 5 mol % catalyst loadings, respectively, significantly lower than that (96%) of 4-methoxyphenyl chloride (**2e**) with 3 mol % catalyst loading (Table 3, entries 1 and 2 vs Table 2, entry 4). However, electron-neutral and -deficient aryl tosylates coupled much more effectively with diarylborinic acids. For example, electron-neutral phenyl (**4c**) and *p*-tolyl (**4d**) tosylates reacted with **1a**

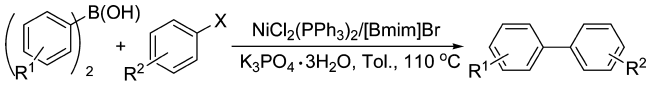
dx.doi.org/10.1021/jo501291y | J. Org. Chem. 2014, 79, 7132−7140

afforded the corresponding biaryls **6ac** and **3ab** in 87 and 88% yields, respectively (Table 3, entries 4 and 5). The reaction of 4-acetylphenyl tosylate (**4f**) occurred to afford **3ao** in 88 and 93% yields with 1.5 or 3 mol % $NiCl_2(PPh_3)_2$/[Bmim]Br, respectively, just slightly lower than that (98%) of 4-acetylphenyl chloride (**2o**) (Table 3, entries 7 and 8 vs Table 2, entry 15). The steric effects observed for both aryl tosylates and diarylborinic acids bearing a small *ortho*-substituent were negligible. For example, the reactions of bis(*p*-tolyl)borinic acid (**1a**) with 2-methoxyphenyl tosylate (**4b**) and 2-methylphenyl tosylate (**4e**) gave products **3af** (62%) and **3ac** (85%) in yields comparable to those (68%, **4a** and 88%, **4d**) with a *para*-substituent (Table 3, entries 2, 3, 5 and 6). Similarly, diarylborinic acids with an *ortho*-substituent at aromatic rings, such as *o*-methyl (**1e**), *o*-ethyl (**1f**), *o*-methoxy (**1g**) or even *o*-isopropoxy (**1h**) reacted with 4-acetylphenyl tosylate (**4f**) as well as those without an *ortho*-substituent **1a** and **1c** (Table 3, entries 8, 10 and 13−16).

Aryl dimethylsulfamates coupled with diarylborinic acids similarly to tosylates under the above established conditions although sulfamates are generally believed to be more stable. Electronically deactivated aryl sulfamates reacted even more smoothly than the corresponding tosylates. For example, reaction of bis(*p*-tolyl)borinic acid (**1a**) with electron-rich aryl sulfamate, 4-methoxyphenyl dimethylsulfamate (**5a**), could afford 4-methoxy-4′-methyl biphenyl **3ae** in 79% yield with 5 mol % catalyst loading, slightly higher than that (68%) of aryl tosylate **4a** under otherwise identical conditions (Table 3, entries 2 and 17). The higher reactivity of sulfamates over tosylates could be possibly attributed to an intramolecular N−Ni coordination between the sulfamate group and the catalyst, which should facilitate the oxidative addition of Aryl-OSO_2NMe_2. For electron-deficient aryl sulfamates, such as 4-acetylphenyl dimethylsulfamate **5f**, 1.5 mol % catalyst loading proved enough for it to couple with bis(*p*-tolyl)borinic acid **1a**, affording the desired product **3ao** in an excellent yield (91%) (Table 3, entry 23). Similar to the reaction of aryl tosylates, steric effects from both aryl sulfamates and diarylborinic acids with a small *ortho*-substituent on the aromatic rings appeared to be negligible since all of the investigated substrates with an *ortho*-substituent, e.g., diarylborinic acids **1e** (2-Me), **1f** (2-Et), **1g** (2-OMe), or **1h** (2-O^{i}Pr), and aryl sulfamates **5b** (2-OMe) and **5e** (2-Me) reacted comparably to those without an *ortho*-substituent to give the desired biaryls (**3af**, **3ac** and **6ea**−**6hf**) in good to excellent yields (Table 3, entries 18, 21 and 26-31).

Application Exploration. Synthesis of Adapalene, a member of the new generation synthetic receptor-selective retinoids,[24] is taken here as an illustrative example for application of the $NiCl_2(NHC)(PPh_3)_2$-catalyzed cross-couplings of aryl tosylates and sulfamates with diarylborinic acids in practical synthesis of biaryl fine chemicals (Scheme 1).[25] The key in synthesis of Adapalene is the connection between 2-(1-adamantyl)anisole and 2-naphthoic acid moieties, which has been effected by cross-coupling of zincate (Negishi),[26] Grignard reagent (Kumada),[27] or boronic acid derivatives (Suzuki)[28] of 2-(1-adamantyl)-4-bromoanisole with 6-bromo-2-naphthoate or 6-tosyloxy-2-naphthoate. Unfortunately, the environmentally friendly Suzuki coupling processes have to be abandoned in commercial production of Adapalene because of the high cost of 3-(1-adamantyl)-4-methoxyphenyl boronic acid, which has to be prepared using either cryogenic conditions or expensive borylation reagents, such as catecholborane or bis(pinacolato)diboron.

Table 3. Scope of the Couplings of Diarylborinic Acids with Aryl Tosylates and Dimethylsulfamates[a]



1a-h 4a-f/5a-f 3ab-ao/6ac-hf

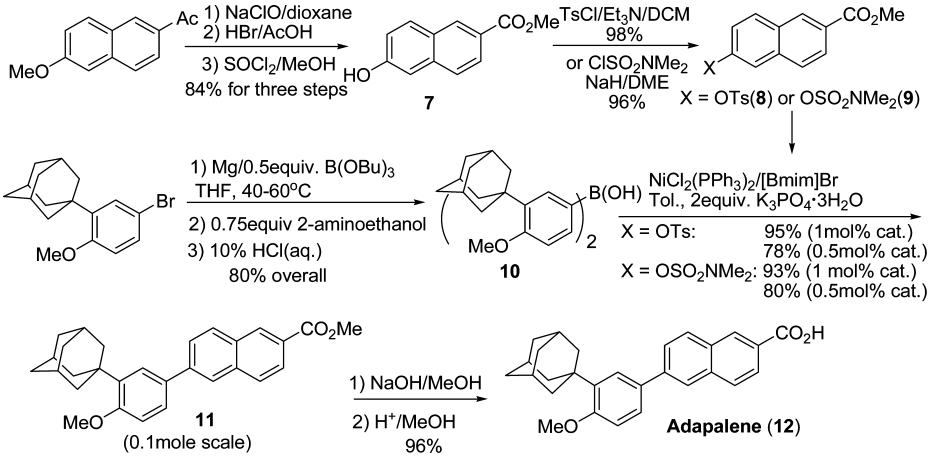
entry	R^1 (1)	X	R^2 (4/5)	cat (mol %)	yield (%)[b]
1	4-Me (**1a**)	OTs	4-OMe (**4a**)	3	47 (**3ae**)
2	4-Me (**1a**)	OTs	4-OMe (**4a**)	5	68 (**3ae**)
3	4-Me (**1a**)	OTs	2-OMe (**4b**)	5	62 (**3af**)
4	4-Me (**1a**)	OTs	H (**4c**)	5	87 (**6ac**)
5	4-Me (**1a**)	OTs	4-Me (**4d**)	5	88 (**3ab**)
6	4-Me (**1a**)	OTs	2-Me (**4e**)	5	85 (**3ac**)
7	4-Me (**1a**)	OTs	4-Ac (**4f**)	3	93 (**3ao**)
8	4-Me (**1a**)	OTs	4-Ac (**4f**)	1.5	88 (**3ao**)
9	4-Me (**1a**)	OTs	4-Ac (**4f**)	1	75 (**3ao**)
10	4-OMe (**1c**)	OTs	4-Ac (**4f**)	1.5	90 (**6cf**)
11	2-Me (**1e**)	OTs	4-OMe (**4a**)	5	65 (**6ea**)
12	2-Me (**1e**)	OTs	H (**4c**)	5	83 (**6ec**)
13	2-Me (**1e**)	OTs	4-Ac (**4f**)	1.5	92 (**6ef**)
14	2-Et (**1f**)	OTs	4-Ac (**4f**)	1.5	89 (**6ff**)
15	2-OMe (**1g**)	OTs	4-Ac (**4f**)	1.5	91 (**6gf**)
16	2-O^{i}Pr (**1h**)	OTs	4-Ac (**4f**)	1.5	89 (**6hf**)
17	4-Me (**1a**)	OSO_2NMe_2	4-OMe (**5a**)	5	79 (**3ae**)
18	4-Me (**1a**)	OSO_2NMe_2	2-OMe (**5b**)	5	80 (**3af**)
19	4-Me (**1a**)	OSO_2NMe_2	H (**5c**)	5	89 (**6ac**)
20	4-Me (**1a**)	OSO_2NMe_2	4-Me (**5d**)	5	83 (**3ab**)
21	4-Me (**1a**)	OSO_2NMe_2	2-Me (**5e**)	5	81 (**3ac**)
22	4-Me (**1a**)	OSO_2NMe_2	4-Ac (**5f**)	3	95 (**3ao**)
23	4-Me (**1a**)	OSO_2NMe_2	4-Ac (**5f**)	1.5	91 (**3ao**)
24	4-Me (**1a**)	OSO_2NMe_2	4-Ac (**5f**)	1	77 (**3ao**)
25	4-OMe (**1c**)	OSO_2NMe_2	4-Ac (**5f**)	1.5	87 (**6cf**)
26	2-Me (**1e**)	OSO_2NMe_2	4-OMe (**5a**)	5	86 (**6ea**)
27	2-Me (**1e**)	OSO_2NMe_2	H (**5c**)	5	90 (**6ec**)
28	2-Me (**1e**)	OSO_2NMe_2	4-Ac (**5f**)	1.5	95 (**6ef**)
29	2-Et (**1f**)	OSO_2NMe_2	4-Ac (**5f**)	1.5	93 (**6ff**)
30	2-OMe (**1g**)	OSO_2NMe_2	4-Ac (**5f**)	1.5	90 (**6gf**)
31	2-O^{i}Pr (**1h**)	OSO_2NMe_2	4-Ac (**5f**)	1.5	86 (**6hf**)

[a]Reaction conditions: **1** (1.3 mmol), **4**/**5** (2 mmol), $K_3PO_4·3H_2O$ (5.2 mmol), toluene (5 mL), N_2, 10 h. [b]Isolated yield.

In contrast, di(3-(1-adamantyl)-4-methoxyphenyl)borinic acid (**10**) could be readily prepared in 80% yield via one-pot reaction from 2-(1-adamantyl)-4-bromoanisole, 1.1 equiv of magnesium and 0.5 equiv of tributylborate in THF at 40−60 °C. The advantages of using *β*-naphthalenyl tosylates and sulfamates over halides in transition metal-catalyzed cross-coupling are obvious because *β*-naphthalenylols are readily available while tedious procedures are often necessary for synthesis of *β*-halonaphthalene derivatives. For example, because of the overwhelming *α*-selectivity in direct halogenation of naphthalenes, *β*-naphthalenyl bromides had to be prepared from *β*-naphthalenylols via bromination using $P(Br_2)Ph_3$ at >250 °C[29] or $Na_2S_2O_5$-mediated OH-NH_2 exchange with NH_4OH (aq.) in autoclave followed by diazotization-bromination with CuBr (Sandmeyer reaction).[30] Methyl 6-tosyloxy-2-naphthoate (**8**) and methyl 6-(dimethylsulfamayl)oxy-2-naphthoate (**9**) were prepared in 82 and 81% yields, respectively, from commercially available 1-(6-methoxynaphthalen-2-yl)ethanone[31] via a 4-step, chromatography-free process consisting of chloroform reaction, demethylation in HBr/AcOH, esterization and tosylation or

dx.doi.org/10.1021/jo501291y | J. Org. Chem. 2014, 79, 7132−7140

Scheme 1. Scalable and Cost-Effective Process for Synthesis of Adapalene



sulfamation. The cross-coupling of di(3-(1-adamantyl)-4-methoxyphenyl)borinic acid (**10**) with methyl 6-tosyloxy-2-naphthoate (**8**) or methyl 6-(dimethylsulfamayl)oxy-2-naphthoate (**9**) proceeded smoothly to provide methyl ester of Adapalene (**11**) in 95 and 93% yields, respectively, with 1 mol % $NiCl_2(PPh_3)_2$/[Bmim]Br as catalyst precursor in 0.1 mol scale, from which Adapalene (**12**) could be readily obtained after hydrolysis.

CONCLUSION

In summary, cross-couplings of diarylborinic acids with aryl chlorides, tosylates, and sulfamates have been efficiently effected by using a simple mono(NHC)bis(phosphine)nickel catalyst system generated in situ from $NiCl_2(PPh_3)_2$ and dialkylimidazoliums in the presence of $K_3PO_4·3H_2O$ as base in toluene. In contrast to bis(NHC)nickel-catalyzed conventional Suzuki coupling of arylboronic acids, mono(NHC)bis(phosphine)nickel species of sterically undemanding *N*,*N*′-dialkylimidazolylidene displayed high catalytic activities in the cross-couplings of diarylborinic acids. Scope and limitation of the mono(NHC)bis(phosphine)nickel-catalyzed couplings have been briefly explored. Structural influences from diarylborinic acids appeared to be negligible in the cross-couplings while remarkable electronic effects have been observed from aryl chlorides, tosylates, and sulfamates. For electronically activated aryl chlorides, 1.5 mol % catalyst loading proved enough in their couplings with diarylborinic acids to give the biaryl products in excellent yields while 3 mol % $NiCl_2(PPh_3)_2$/[Bmim]Br had to be used for the coupling of deactivated ones. For aryl tosylates and sulfamates, a larger electronic influence than that from aryl chlorides was observed in their couplings. A higher catalyst loading (5 mol %) had to be used to obtain the biaryl products in modest to good yields for non- or deactivated tosylates and sulfamates while 1.5 mol % loading worked well in the couplings of those bearing an electron-withdrawing group. A small *ortho*-substitutent on the aromatic ring of aryl chlorides, tosylates, and sulfamates showed negligible influences on their cross-coupling reactions. Features of the mono(NHC)bis(phosphine)nickel-catalyzed cross-couplings include high atom and process economies of diarylborinic acids, readily available aryl (pseudo)halides and cost-effectiveness of nickel catalyst system, which have been demonstrated in development of practical processes for synthesis of a third-generation topical retinoid, Adapalene.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under a N_2 atmosphere unless otherwise stated. Commercially available chemicals were used as received. Nickel complexes of $NiCl_2(PPh_3)_2$,[32] $NiCl_2[(4\text{-}MeOPh)_3P]_2$,[32] $NiCl_2(PCy_3)_2$,[23a] $NiCl_2$(dppm),[33] $NiCl_2$(dppe),[33] $NiCl_2$(dppp),[33] $NiCl_2$(dppb),[33] and $NiCl_2$(dppf);[34] N-heterocyclic carbene precursors of [Bmim]Br,[35] [Emim]Br,[35] [Pmim]Br,[35] [Hmim]Br,[35] [diMim]I,[35] [diBim]Br,[35] [di^{t}Buim]Cl,[35] [^{t}Bumim]I,[35] IPr·HCl,[8a] IMes·HCl,[8a] IPh·HCl,[36] [Phmim]I,[37] and [Mesmim]I,[37] diarylborinic acids,[6a] aryl tosylates,[23b] aryl sulfamates[2e] and 2-(1-adamantyl)-4-bromoanisole[38] were prepared according to previously reported procedures. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at ambient temperature. Chemical shifts in NMR are reported in ppm (δ), relative to the internal standard of tetramethylsilane (TMS). The signals observed are described as s (singlet), d (doublet), t (triplet), dd (double doublet), m (multiplets). The number of protons (n) for a given resonance is indicated as nH. Coupling constants are reported as J in Hz.

General Procedure for Cross-Couplings of Aryl Chlorides, Tosylates, and Sulfamates. *For Aryl Chlorides.* To a 10 mL flask were added aryl chloride (2.0 mmol), diarylborinic acid (1.3 mmol), 1.5−3 mol % $NiCl_2(PPh_3)_2$ (0.03−0.06 mmol), 1.5−3 mol % [Bmim]Br (0.03−0.06 mmol), $K_3PO_4·3H_2O$ (5.2 mmol), and toluene (5 mL). The mixture was stirred at 110 °C for a given time or monitored by TLC until the starting material was completely consumed. The reaction mixture was diluted with CH_2Cl_2 (15 mL). The organic layer was separated and washed with H_2O (10 mL × 2), followed by drying over Na_2SO_4, filtering and removal of solvents under reduced pressure to give the crude product, which was purified by column chromatography on silica gel with EtOAc/petroleum ether.

For aryl Tosylates and Sulfamates. A procedure similar to that for the cross-coupling of aryl chlorides was adopted with aryl tosylates and dimethylsulfamates using 1−5 mol % catalyst loadings.

4-Benzyloxy-4′-methylbipheny (3aa).[6a] White solid (0.510 g, 93%): mp 140−142 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.36 (m, 6H), 7.32 (t, J = 7.6 Hz, 2H), 7.25 (t, J = 7.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 5.01 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 138.0, 137.1, 136.4, 134.0, 129.5, 128.7, 128.0, 127.6, 126.7, 115.2, 70.1, 21.2.

4,4′-Dimethylbiphenyl (3ab).[6a] White solid (0.357 g, 98% from aryl chloride **2b**, 0.320 g, 88% from aryl tosylate **4d**, 0.302 g, 83% from aryl sulfamate **5d**): mp 122−123 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.0 Hz, 4H), 7.22 (d, J = 8.0 Hz, 4H), 2.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 136.8, 129.5, 126.9, 21.2.

2,4′-Dimethylbiphenyl (3ac).[6a] Colorless oil (0.346 g, 95% from aryl chloride **2c**, 0.309 g, 85% from aryl tosylate **4e**, 0.295 g, 81% from aryl sulfamate **5e**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.26−7.22 (m, 8H), 2.40 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

dx.doi.org/10.1021/jo501291y | J. Org. Chem. 2014, 79, 7132−7140

141.9, 139.0, 136.4, 135.4, 130.3, 129.9, 129.1, 128.8, 127.1, 125.8, 21.2, 20.5.

2,6,4′-Trimethylbiphenyl (3ad).[39] Colorless oil (0.129 g, 33%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.25 (m, 3H), 7.21−7.13 (m, 3H), 7.07 (d, J = 8.0 Hz, 1H), 2.44 (s, 3H), 2.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 138.0, 136.3, 136.1, 129.1, 128.9, 127.2, 126.9, 21.3, 20.9.

4-Methoxy-4′-methylbiphenyl (3ae).[6a] White solid (0.380 g, 96% from aryl chloride **2e**, 0.269 g, 68% from aryl tosylate **4a**, 0.313 g, 79% from aryl sulfamate **5a**): mp 111−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 138.0, 136.4, 133.8, 129.5, 128.0, 126.6, 114.2, 55.4, 21.1.

2-Methoxy-4′-methylbiphenyl (3af).[6a] White solid (0.368 g, 93% from aryl chloride **2f**, 0.246 g, 62% from aryl tosylate **4b**, 0.317 g, 80% from aryl sulfamate **5b**): mp 79−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.00 (t, J = 7.6 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 3.79 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 136.6, 135.6, 130.8, 130.7, 129.5, 128.8, 128.4, 120.8, 111.2, 55.6, 21.3.

2-Isopropoxy-4′-methylbiphenyl (3ag). Colorless oil (0.284 g, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 2H), 7.38 (dd, J = 1.6, 7.6 Hz, 1H), 7.33−7.29 (m, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.08−7.02 (m, 2H), 4.52−4.46 (m, 1H), 2.45 (s, 3H), 1.31 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 136.3, 136.0, 132.0, 131.1, 129.5, 128.6, 128.2, 121.0, 115.2, 70.9, 22.1, 21.3; HRMS (ESI-TOF) m/z $[M+1]^+$ calcd for $C_{16}H_{19}O$ 227.1436, found 227.1436.

***N*,*N*,4′-Trimethylbiphenyl-4-amine (3ah).**[6a] Yellow solid (0.388 g, 92%): mp 149−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.44 (m, 4H), 7.20 (d, J = 7.6 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 2.97 (s, 6H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 138.4, 135.7, 129.4, 127.6, 126.2, 113.0, 40.7, 21.1.

4-Methyl-4′-aminobiphenyl (3ai).[6a] Yellow solid (0.304 g, 83%): mp 92−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 3.63 (br, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 138.4, 136.0, 131.6, 129.5, 127.9, 126.4, 115.5, 21.1.

4-Methyl-2′-aminobiphenyl (3aj).[6a] Colorless oil (0.289 g, 79%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.14−7.10 (m, 2H), 6.80 (t, J = 7.2 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 3.51 (br, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 136.9, 136.6, 130.5, 129.6, 129.0, 128.4, 127.7, 118.7, 115.6, 21.2.

4-Cyano-4′-methylbiphenyl (3ak).[6a] White solid (0.367 g, 95%): mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4H), 7.48 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 138.8, 136.3, 132.6, 129.9, 127.5, 127.1, 119.1, 110.5, 21.2.

3-Cyano-4′-methylbiphenyl (3al).[6a] Yellow solid (0.359 g, 93%): mp 73−74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 138.4, 136.0, 131.3, 130.5, 130.4, 129.9, 129.6, 126.9, 119.0, 112.9, 21.2.

2-Cyano-4′-methylbiphenyl (3am).[6a] White solid (0.374 g, 97%): mp 49−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.51−7.39 (m, 4H), 7.30 (d, J = 8.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 138.7, 135.3, 133.8, 132.9, 130.1, 129.5, 128.7, 127.4, 119.0, 111.1, 21.3.

1-(4′-Methylbiphenyl-2-yl)ethanone (3an).[6a] Colorless oil (0.395 g, 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.48 (m, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.23 (s, 4H), 2.41 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 140.9, 140.5, 137.8, 130.7, 130.2, 129.4, 128.8, 127.8, 127.2, 30.5, 21.2.

1-(4′-Methylbiphenyl-4-yl)ethanone (3ao).[6a] White solid (0.412 g, 98% from aryl chloride **2o**, 0.391 g, 93% from aryl tosylate **4f**, 0.399 g, 95% from aryl sulfamate **5f**): mp 118−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 2.0, 8.4 Hz, 2H), 7.66 (dd, J = 2.0, 8.4 Hz, 2H), 7.53 (dd, J = 2.0, 8.0 Hz, 2H), 7.28 (d, J = 6.4 Hz, 2H), 2.63 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 145.7, 138.3, 136.9, 135.6, 129.7, 129.0, 127.1, 126.9, 26.7, 21.2.

Methyl 4-methylbiphenyl-4′-carboxylate (3ap).[6a] White solid (0.434 g, 96%): mp 115−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 7.6 Hz, 2H), 3.92 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 145.6, 138.1, 137.1, 130.1, 129.7, 128.6, 127.1, 126.8, 52.1, 21.2.

4-Methylbiphenyl-4′-carboxaldehyde (3aq).[6a] White solid (0.372 g, 95%): mp 105−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 147.2, 138.6, 136.8, 135.0, 130.3, 129.8, 127.4, 127.2, 21.2.

4-Benzyloxybiphenyl (3ba).[6a] White solid (0.489 g, 94%): mp 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.51 (m, 4H), 7.45−7.37 (m, 6H), 7.34−7.27 (m, 2H), 7.04 (d, J = 8.4 Hz, 2H), 5.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 139.7, 135.9, 133.0, 127.7, 127.6, 127.1, 126.9, 126.4, 125.7, 125.6, 114.1, 69.0.

4-Benzyloxy-4′-methoxybiphenyl (3ca).[6a] White solid (0.522 g, 90%): mp 172−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.37 (m, 6H), 7.32 (t, J = 7.2 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 6.95 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.02 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 156.9, 136.0, 132.7, 132.4, 128.3, 127.6, 126.9, 126.7, 126.5, 114.1, 113.1, 69.1, 54.3.

4-Benzyloxy-4′-fluorobiphenyl (3da).[6a] White solid (0.489 g, 88%): mp 139−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.36 (m, 6H), 7.31 (t, J = 7.4 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 7.00 (t, J = 8.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 5.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1 (d, J = 250 Hz), 157.3, 135.9, 132.0, 127.6, 127.2, 127.1, 127.0, 126.4, 114.5 (d, J = 21 Hz), 114.1, 69.0.

4-Benzyloxy-2′-methylbiphenyl (3ea).[6a] White solid (0.493 g, 90%): mp 62−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.35−7.31 (m, 1H), 7.26−7.21 (m, 6H), 7.02 (d, J = 8.8 Hz, 2H), 5.09 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 140.4, 135.9, 134.3, 133.5, 129.2, 129.1, 128.8, 127.5, 126.8, 126.4, 125.9, 124.7, 113.3, 68.8, 19.5.

4-Benzyloxy-2′-ethylbiphenyl (3fa).[6a] Colorless oil (0.484 g, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.2 Hz, 2H), 7.42−7.38 (m, 2H), 7.35−7.33 (m, 1H), 7.29−7.28 (m, 2H), 7.24−7.17 (m, 4H), 7.01 (d, J = 8.8 Hz, 2H), 5.09 (s, 2H), 2.61 (q, J = 7.6 Hz, 2H), 1.10 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 141.8, 141.3, 137.1, 134.7, 130.3, 130.2, 128.7, 128.6, 128.1, 127.6, 127.3, 125.6, 114.4, 70.1, 26.2, 15.7.

4-Benzyloxy-2′-methoxybiphenyl (3ga).[6a] Colorless oil (0.510 g, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, J = 8.2 Hz, 4H), 7.38 (t, J = 7.4 Hz, 2H), 7.33−7.26 (m, 3H), 7.02−6.94 (m, 4H), 5.08 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 156.5, 137.2, 131.2, 130.8, 130.7, 130.3, 128.7, 128.3, 128.0, 127.6, 120.9, 114.5, 111.2, 70.1, 55.6.

4-Benzyloxy-2′-isopropoxybiphenyl (3ha).[6a] Colorless oil (0.566 g, 89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.45 (m, 4H), 7.39 (t, J = 7.4 Hz, 2H), 7.34−7.29 (m, 2H), 7.25−7.21 (m, 1H), 7.02−6.95 (m, 4H), 5.09 (s, 2H), 4.47−4.37 (m, 1H), 1.24 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 154.9, 137.2, 131.7, 131.6, 130.9, 130.7, 128.6, 128.0, 127.6, 121.1, 115.4, 114.2, 70.9, 70.0, 22.1.

2-Methoxy-2′-methylbiphenyl (3ef).[6a] Colorless oil (0.285 g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, J = 8.4 Hz, 1H), 7.24−7.13 (m, 5H), 6.99 (t, J = 7.6 Hz, 1H), 6.94 (t, J = 8.4 Hz, 1H), 3.73 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 138.7, 136.9, 131.1, 130.9, 130.1, 129.6, 128.6, 127.4, 125.5, 120.5, 110.7, 55.4, 20.0.

2-Methoxy-2′-ethylbiphenyl (3ff).[6a] Colorless oil (0.229 g, 54%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.29 (m, 3H), 7.24−7.19 (m, 1H), 7.15−7.13 (m, 2H), 6.98 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 3.71 (s, 3H), 2.50−2.41 (m, 2H), 1.06 (t, J = 7.4 Hz,

dx.doi.org/10.1021/jo501291y | J. Org. Chem. 2014, 79, 7132−7140

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 142.8, 138.1, 131.3, 130.8, 130.2, 128.6, 127.9, 127.6, 125.5, 120.4, 110.7, 55.4, 26.2, 15.1.

2,2′-Dimethoxybiphenyl (3gf).[40] White solid (0.304 g, 71%): mp 153−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.38 (m, 2H), 7.34−7.31 (m, 2H), 7.10−7.04 (m, 4H), 3.84 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 131.5, 128.7, 127.8, 120.4, 111.1, 55.7.

2-Methoxy-2′-isopropoxybiphenyl (3hf).[6a] Colorless oil (0.315 g, 65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 4H), 7.06−6.98 (m, 4H), 4.47−4.38 (m, 1H), 3.81 (s, 3H), 1.22 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 155.5, 131.7, 131.6, 129.4, 128.4, 128.3, 128.2, 120.5, 120.1, 114.9, 110.7, 70.8, 55.5, 22.1.

4-Methylbiphenyl (6ac).[5d] White solid (0.292 g, 87% from aryl tosylate **4c**, 0.299 g, 89% from aryl sulfamate **5c**): mp 45−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 7.6 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 138.5, 137.1, 129.6, 128.8, 127.1, 21.2.

1-(4′-Methoxybiphenyl-4-yl)ethanone (6cf).[5d] White solid (0.407 g, 90% from aryl tosylate **4f**, 0.394 g, 87% from aryl sulfamate **5f**): mp 156−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 159.9, 145.3, 135.2, 132.2, 129.0, 128.4, 126.6, 114.4, 55.4, 26.7.

4-Methoxy-2′-methylbiphenyl (6ea).[41] White solid (0.257 g, 65% from aryl tosylate **4a**, 0.341 g, 86% from aryl sulfamate **5a**): mp 51−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.21 (m, 6H), 6.95 (d, J = 8.4 Hz, 2H), 3.85 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 141.6, 135.5, 134.4, 130.31, 130.27, 129.9, 127.0, 125.8, 113.5, 55.3, 20.6.

2-Methylbiphenyl (6ec).[41] Colorless oil (0.279 g, 83% from aryl tosylate **4c**, 0.302 g, 90% from aryl sulfamate **5c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, J = 7.2 Hz, 2H), 7.34−7.31 (m, 3H), 7.26−7.23 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 135.4, 130.4, 129.9, 129.3, 128.2, 127.3, 126.8, 125.9, 20.6.

1-(2′-Methylbiphenyl-4-yl)ethanone (6ef).[5d] Colorless oil (0.386 g, 92% from aryl tosylate **4f**, 0.399 g, 95% from aryl sulfamate **5f**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.31−7.21 (m, 4H), 2.65 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 147.0, 140.8, 135.6, 135.2, 130.6, 129.6, 129.5, 128.3, 128.0, 126.0, 26.7, 20.5.

1-(2′-Ethylbiphenyl-4-yl)ethanone (6ff).[42] Colorless oil (0.399 g, 89% from aryl tosylate **4f**, 0.417 g, 93% from aryl sulfamate **5f**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.34−7.33 (m, 2H), 7.27−7.23 (m, 1H), 7.18 (d, J = 7.6 Hz, 1H), 2.65 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 1.09 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 147.1, 141.4, 140.5, 135.6, 129.6, 129.5, 128.8, 128.2, 128.1, 125.8, 26.7, 26.1, 15.7.

4-Acetyl-2′-methoxybiphenyl (6gf).[43] White solid (0.411 g, 91% from aryl tosylate **4f**, 0.407 g, 90% from aryl sulfamate **5f**): mp 105−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.38−7.32 (m, 2H), 7.05 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 156.5, 143.6, 135.5, 130.7, 129.8, 129.5, 129.4, 128.1, 121.0, 111.3, 55.6, 26.7.

4-Acetyl-2′-isopropoxybiphenyl (6hf). White solid (0.452 g, 89% from aryl tosylate **4f**, 0.437 g, 86% from aryl sulfamate **5f**): mp 75−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.35−7.29 (m, 2H), 7.04−6.99 (m, 2H), 4.54−4.44 (m, 1H), 2.63 (s, 3H), 1.26 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 154.9, 144.0, 135.3, 131.0, 130.6, 129.8, 129.3, 128.0, 121.0, 114.8, 70.9, 26.7, 22.0; HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{17}H_{18}O_2$ 254.1307, found 254.1306.

Methyl 6-hydroxy-2-naphthoate (7).[44] White solid (34.0 g, 84% from 1-(6-methoxynaphthalen-2-yl)ethanone (0.2 mol scale)): mp 168−170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.52 (s, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.89 (dd, J = 1.2, 8.8 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.23−7.19 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 157.7, 137.1, 131.2, 130.5, 126.6, 126.4, 125.0, 123.6, 119.6, 108.7, 51.9.

Methyl 6-tosyloxy-2-naphthoate (8).[45] White solid (58.7 g, 98%): mp 102−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57(s, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.53 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.16 (dd, J = 2.0, 8.8 Hz, 1H), 3.98 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 148.9, 145.7, 135.7, 132.3, 131.3, 130.9, 130.7, 129.9, 128.5, 128.1, 128.0, 126.3, 122.1, 119.9, 52.4, 21.7.

Methyl 6-(dimethylsulfamayl)oxy-2-naphthoate (9).[23g] White solid (49.9 g, 96%): mp 115−117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71(s, 1H), 8.29 (d, J = 9.2 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.05 (d, J = 8.8 Hz, 1H), 8.01 (d, J = 1.6 Hz, 1H), 7.59 (dd, J = 2.0, 8.8 Hz, 1H), 3.94 (s, 3H), 2.98 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 149.2, 135.5, 131.8, 130.5, 130.4, 128.4, 127.3, 125.8, 122.0, 118.9, 52.3, 38.3.

Synthesis of Di(3-(1-adamantyl)-4-methoxyphenyl)borinic acid (10). Under a N_2 atmosphere, a mixture of $B(OBu)_3$ (23.02 g, 100 mmol) and 2-(1-adamantyl)-4-bromoanisole (64.25 g, 200 mmol) in 100 mL of THF was added dropwise to a stirred mixture of magnesium turnings (5.28 g, 220 mmol) and a small crystal of I_2 in THF (50 mL) at 40 °C over a period of 30 min. The reaction was maintained at 40−60 °C for an additional 2 h and then hydrolyzed by the addition of 200 mL of 5% HCl (aq.) after being cooled to room temperature. The mixture was extracted with EtOAc and then concentrated to 40 mL before 2-ethanolamine (9.16 g, 150 mmol) was added. The resulting solution was stirred at room temperature for 2 h and then washed with water. The organic layer was concentrated under a vacuum to obtain the crude product of 2-aminoethoxydi(3-(1-adamantyl)-4-methoxyphenyl)borate, which was recrystallized in ethanol and then acidified with 100 mL of 10% HCl (aq). The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under a vacuum to afford di(3-(1-adamantyl)-4-methoxyphenyl)borinic acid 39.2 g (80%) as a white crystalline solid: mp 166−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 2H), 7.69 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 5.54 (s, 1H), 3.89 (s, 6H), 2.13 (s, 12H), 2.06 (s, 6H), 1.77 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 137.5, 134.1, 133.8, 111.1, 54.9, 40.7, 37.2, 37.1, 29.1; HRMS (ESI-TOF) m/z $[M]^+$ calcd for $C_{34}H_{43}BO_3$ 510.3305, found 510.3336.

Methyl 6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoate (11).[27b] White solid (40.5 g, 95% from aryl tosylate **8**, 39.7 g, 93% from aryl sulfamate **9**): mp 226−229 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.07 (dd, J = 1.2, 8.4 Hz, 1H), 8.01−7.98 (m, 2H), 7.92 (d, J = 8.8 Hz, 1H), 7.79 (dd, J = 1.6, 8.8 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.54 (dd, J = 2.4, 8.4 Hz, 1H), 7.00 (s, 1H), 3.99 (s, 3H), 3.90 (s, 3H), 2.18 (s, 6H), 2.10 (s, 3H), 1.80 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 158.9, 141.4, 139.0, 136.0, 132.6, 131.3, 130.9, 129.7, 128.2, 126.9, 126.5, 126.0, 125.8, 125.6, 124.8, 112.1, 55.2, 52.2, 40.6, 37.23, 37.16, 29.1.

0.1 Mole Scale Synthesis of Adapalene (12).[27b] Under a N_2 atmosphere, to a 500 mL flask were added methyl 6-tosyloxy-2-naphthoate (35.6 g, 0.1 mol), di(3-(1-adamantyl)-4-methoxyphenyl)-borinic acid (33.2 g, 0.065 mol), $NiCl_2(PPh_3)_2$ (0.65 g, 0.001 mol), [Bmim]Br (0.22 g, 0.001 mol), $K_3PO_4{\cdot}3H_2O$ (53.3 g, 0.2 mol), and toluene (250 mL). The mixture was stirred at 110 °C for 10 h. The solid materials were filtrated off while keeping hot and washed with 100 mL of toluene. The filtrate was cooled to give methyl ester of Adapalene as a white solid (40.5 g, 95%), which was hydrolyzed with NaOH (10% aq.) and acidified with dilute HCl (5% aq.) to afford the desired product Adapalene as a white crystalline solid (37.6 g, 96%): mp 320−321 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.22 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 7.13 (d, J = 8.8 Hz, 1H), 3.87 (s, 3H), 2.14 (s, 6H), 2.07 (s, 3H), 1.76 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.6, 158.5, 140.1, 138.0, 135.4, 131.5, 130.9, 130.1, 129.7, 128.2, 128.1, 125.8, 125.7, 125.6, 125.0, 124.0, 112.6, 55.3, 40.0, 36.5, 28.4.

dx.doi.org/10.1021/jo501291y | J. Org. Chem. 2014, 79, 7132−7140

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zougang@ecust.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support provided by the National Science Foundation of China (No. 20972049).

■ REFERENCES

(1) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6723−6737. (c) Li, H.; Johansson Seechurn, C. C. C.; Colacot, T. J. *ACS Catal.* **2012**, *2*, 1147−1164. (d) Lennox, A. J. J.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7362−7370.

(2) (a) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060−1065. (b) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447−3452. (c) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346−1416. (d) Leowanawat, P.; Zhang, N.; Resmerita, A.-M.; Rosen, B. M.; Percec, V. *J. Org. Chem.* **2011**, *76*, 9946−9955. (e) Leowanawat, P.; Zhang, N.; Percec, V. *J. Org. Chem.* **2012**, *77*, 1018−1025. (f) Leowanawat, P.; Zhang, N.; Safi, M.; Hoffman, D. J.; Fryberger, M. C.; George, A.; Percec, V. *J. Org. Chem.* **2012**, *77*, 2885−2892. (g) Zhang, N.; Hoffman, D. J.; Gutsche, N.; Gupta, J.; Percec, V. *J. Org. Chem.* **2012**, *77*, 5956−5964.

(3) (a) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027−11029. (b) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908−11909. (c) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362−15364. (d) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154−8157. (e) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794−5797. (f) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624−627.

(4) Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270−5298.

(5) (a) Hall, D. G., Ed.; *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine*; Wiley-VCH: Weinheim, 2005. (b) Cole, T. E.; Haly, B. D. *Organometallics* **1992**, *11*, 652−657. (c) Brown, H. C.; Racherla, U. S. *J. Org. Chem.* **1986**, *51*, 427−432. (d) Chen, X.; Ke, H.; Chen, Y.; Guan, C.; Zou, G. *J. Org. Chem.* **2012**, *77*, 7572−7578.

(6) (a) Chen, X.; Ke, H.; Zou, G. *ACS Catal.* **2014**, *4*, 379−385. (b) Ke, H.; Chen, X.; Feng, Y.; Zou, G. *Sci. China Chem.* **2014**, DOI: 10.1007/s11426-014-5138-3.

(7) (a) Radius, U.; Bickelhaupt, F. M. *Coord. Chem. Rev.* **2009**, *253*, 678−686. (b) Jacobsen, H.; Correa, A.; Poater, A.; Costabile, C.; Cavallo, L. *Coord. Chem. Rev.* **2009**, *253*, 687−703.

(8) (a) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470−5472. (b) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194−16195. (c) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101−4111. (d) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440−1449. (e) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151−5169. (f) Chartoire, A.; Lesieur, M.; Falivene, L.; Slawin, A. M. Z.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P. *Chem.—Eur. J.* **2012**, *18*, 4517−4521. (g) Meiries, S.; Duc, G. L.; Chartoire, A.; Collado, A.; Speck, K.; Arachchige, K. S. A.; Slawin, A. M. Z.; Nolan, S. P. *Chem.—Eur. J.* **2013**, *19*, 17358−17368.

(9) (a) Valente, C.; Baglione, S.; Candito, D.; O'Brien, C. J.; Organ, M. G. *Chem. Commun.* **2008**, 735−737. (b) Organ, M. G.; Çalimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2383−2387. (c) Nasielski, J.; Hadei, N.; Achonduh, G.; Kantchev, E. A. B.; O'Brien, C. J.; Lough, A.; Organ, M. G. *Chem.—Eur. J.* **2010**, *16*, 10844−10853. (d) Farmer, J. L.; Hunter, H. N.; Organ, M. G. *J. Am. Chem. Soc.* **2012**, *134*, 17470−17473. (e) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314−3332.

(10) (a) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690−3693. (b) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195−15201. (c) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523−1533.

(11) McGuinness, D. S.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 1596−1605.

(12) Zhong, C.; Sasaki, T.; Tada, M.; Iwasawa, Y. *J. Catal.* **2006**, *242*, 357−364.

(13) (a) Schaub, T.; Backes, M.; Radius, U. *J. Am. Chem. Soc.* **2006**, *128*, 15964−15965. (b) Zell, T.; Radius, U. *Z. Anorg. Allg. Chem.* **2011**, *637*, 1858−1862. (c) Zell, T.; Feierabend, M.; Halfter, B.; Radius, U. *J. Organomet. Chem.* **2011**, *696*, 1380−1387. (d) Zell, T.; Fischer, P.; Schmidt, D.; Radius, U. *Organometallics* **2012**, *31*, 5065−5073.

(14) Zhang, K.; Conda-Sheridan, M.; Cooke, S. R.; Louie, J. *Organometallics* **2011**, *30*, 2546−2552.

(15) Oertel, A. M.; Ritleng, V.; Burr, L.; Chetcuti, M. J. *Organometallics* **2011**, *30*, 6685−6691.

(16) (a) Liao, C.-Y.; Chan, K.-T.; Chang, Y.-C.; Chen, C.-Y.; Tu, C.-Y.; Hu, C.-H.; Lee, H. M. *Organometallics* **2007**, *26*, 5826−5833. (b) Lee, C.-C.; Ke, W.-C.; Chan, K.-T.; Lai, C.-L.; Hu, C.-H.; Lee, H. M. *Chem.—Eur. J.* **2007**, *13*, 582−591.

(17) (a) Chiu, P. L.; Lai, C.-L.; Chang, C.-F.; Hu, C.-H.; Lee, H. M. *Organometallics* **2005**, *24*, 6169−6178. (b) Inamoto, K.; Kuroda, J.; Hiroya, K.; Noda, Y.; Watanabe, M.; Sakamoto, T. *Organometallics* **2006**, *25*, 3095−3098. (c) Inamoto, K.; Kuroda, J.; Sakamoto, T.; Hiroya, K. *Synthesis* **2007**, 2853−2861. (d) Inamoto, K.; Kuroda, J.; Kwon, E.; Hiroya, K.; Doi, T. *J. Organomet. Chem.* **2009**, *694*, 389−396. (e) Kuroda, J.; Inamoto, K.; Hiroya, K.; Doi, T. *Eur. J. Org. Chem.* **2009**, 2251−2261. (f) Xi, Z.; Zhang, X.; Chen, W.; Fu, S.; Wang, D. *Organometallics* **2007**, *26*, 6636−6642. (g) Tu, T.; Mao, H.; Herbert, C.; Xu, M.; Dötz, K. H. *Chem. Commun.* **2010**, *46*, 7796−7798. (h) Xu, M.; Li, X.; Sun, Z.; Tu, T. *Chem. Commun.* **2013**, *49*, 11539−11541. (i) Wang, Z.-X.; Liu, N. *Eur. J. Inorg. Chem.* **2012**, 901−911.

(18) Diebolt, O.; Jurčík, V.; da Costa, R. C.; Braunstein, P.; Cavallo, L.; Nolan, S. P.; Slawin, A. M. Z.; Cazin, C. S. J. *Organometallics* **2010**, *29*, 1443−1450.

(19) Chen, M.-T.; Vicic, D. A.; Turner, M. L.; Navarro, O. *Organometallics* **2011**, *30*, 5052−5056.

(20) Ho, C.-Y.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 782−785.

(21) Besides steric hindrance, a coordinative stabilization between carbonyl and nickel ion in the intermediates of ArNi(II)Cl or ArNi(II)Ar′ was proposed to be the other factor hampering the coupling. Inada, K.; Miyaura, N. *Tetrahedron* **2000**, *56*, 8657−8660.

(22) (a) Rappoport, Z., Ed.; *The Chemistry of Phenols*; John Wiley & Sons: Chichester, 2003. (b) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29−39.

(23) (a) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049−3051. (b) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058−3059. (c) Butler, T. A.; Swift, E. C.; Lipshutz, B. H. *Org. Biomol. Chem.* **2008**, *6*, 19−25. (d) Molander, G. A.; Beaumard, F. *Org. Lett.* **2010**, *12*, 4022−4025. (e) Fan, X.-H.; Yang, L.-M. *Eur. J. Org. Chem.* **2011**, 1467−1471. (f) Xing, C.-H.; Lee, J.-R.; Tang, Z.-Y.; Zheng, J. R.; Hu, Q.-S. *Adv. Synth. Catal.* **2011**, *353*, 2051−2059. (g) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748−17749. (h) Baghbanzadeh, M.; Pilger, C.; Kappe, C. O. *J. Org. Chem.* **2011**, *76*, 1507−1510. (i) Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352−6363.

(24) (a) Nagpal, S.; Chandraratna, R. A. S. *Curr. Pharm. Des.* **2000**, *6*, 919−931. (b) Germain, P.; Chambon, P.; Eichele, G.; Evans, R. M.; Lazar, M. A.; Leid, M.; de Lera, A. R.; Lotan, R.; Mangelsdorf, D. J.; Gronemeyer, H. *Pharmacol. Rev.* **2006**, *58*, 712−725.
(25) A patent is pending on the process, Zou, G.; Ke, H.; Duan, G.; Shi, W.; Zhai, J. CN Pat. Appl. 201410201297.8, 2014.
(26) (a) Shroot, B.; Eustache, J.; Bernardon, J.-M. (CIRD Galderma, France) U.S. Pat. Appl. US4717720 A 19880105, 1988. (b) Charpentier, B.; Bernardon, J.-M.; Eustache, J.; Millois, C.; Martin, B.; Michel, S.; Shroot, B. *J. Med. Chem.* **1995**, *38*, 4993−5006. (c) Serrano, J. P. (Medichem, S.A., Spain) U.S. Pat. Appl. US8119834 B2 20120221, 2012.
(27) (a) Shroot, B.; Eustache, J.; Bernardon, J.-M. (CIRD Galderma, France) E.P. Pat. Appl. EP0199636 A1 19861029, 1986. (b) Liu, Z.; Xiang, J. *Org. Process Res. Dev.* **2006**, *10*, 285−288.
(28) (a) Castaldi, G.; Allegrini, P.; Razzetti, G.; Ercoli, M. (Dipharma SpA, Italy) U.S. Pat. Appl. US7345189 B2 20080318, 2008. (b) Terranova, E.; Pascal, J.-C. (CIRD Galderma, France) U.S. Pat. Appl. US7498461 B2 20090303, 2009. (c) Milanese, A.; Gorincioi, E.; Rajabi, M.; Vistoli, G.; Santaniello, E. *Bioorg. Chem.* **2011**, *39*, 151−158.
(29) (a) Pijper, D.; Jongejan, M. G. M.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2008**, *130*, 4541−4552. (b) Kaku, T.; Matsunaga, N.; Ojida, A.; Tanaka, T.; Hara, T.; Yamaoka, M.; Kusaka, M.; Tasaka, A. *Bioorg. Med. Chem.* **2011**, *19*, 1751−1770. (c) Azizian, F.; Field, A. J.; Heron, B. M.; Kilner, C. *Chem. Commun.* **2012**, *48*, 750−752. (d) Schaefer, J. P.; Higgins, J. *J. Org. Chem.* **1967**, *32*, 1607−1608. (e) Blatter, K.; Schlüter, A.-D. *Synthesis* **1989**, 356−359.
(30) (a) Kim, H. M.; Kim, B. R.; An, M. J.; Hong, J. H.; Lee, K. J.; Cho, B. R. *Chem.—Eur. J.* **2008**, *14*, 2075−2083. (b) Kuethe, J. T.; Childers, K. G.; Humphrey, G. R.; Journet, M.; Peng, Z. *Org. Process Res. Dev.* **2008**, *12*, 1201−1208.
(31) 1-(6-Methoxynaphthalen-2-yl)ethanone could also be readily prepared in large scales: Arsenijevic, L.; Arsenijevic, V.; Horeau, A.; Jacques, J. *Org. Synth.* **1973**, *53*, 5−8.
(32) Browning, M. C.; Davies, R. F. B.; Morgan, D. J.; Sutton, L. E.; Venanzi, L. M. *J. Chem. Soc.* **1961**, 4816−4823.
(33) Van Hecke, G. R.; Horrocks, W. D., Jr. *Inorg. Chem.* **1966**, *5*, 1968−1974.
(34) Rudie, A. W.; Lichtenberg, D. W.; Katcher, M. L.; Davison, A. *Inorg. Chem.* **1978**, *17*, 2859−2863.
(35) Chu, Y.; Deng, H.; Cheng, J.-P. *J. Org. Chem.* **2007**, *72*, 7790−7793.
(36) Clavier, H.; Correa, A.; Cavallo, L.; Escudero-Adán, E. C.; Benet-Buchholz, J.; Slawin, A. M. Z.; Nolan, S. P. *Eur. J. Inorg. Chem.* **2009**, 1767−1773.
(37) Su, H.-L.; Pérez, L. M.; Lee, S.-J.; Reibenspies, J. H.; Bazzi, H. S.; Bergbreiter, D. E. *Organometallics* **2012**, *31*, 4063−4071.
(38) Wang, N.; Wang, R.; Shi, X.; Zou, G. *Beilstein J. Org. Chem.* **2012**, *8*, 227−233.
(39) So, C. M.; Yeung, C. C.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7803−7806.
(40) Nising, C. F.; Schmid, U. K.; Nieger, M.; Bräse, S. *J. Org. Chem.* **2004**, *69*, 6830−6833.
(41) Guan, B.-T.; Lu, X.-Y.; Zheng, Y.; Yu, D.-G.; Wu, T.; Li, K.-L.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 396−399.
(42) Ke, H.; Chen, X.; Zou, G. *Appl. Organomet. Chem.* **2014**, *28*, 54−60.
(43) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5359−5363.
(44) Verga, D.; Percivalle, C.; Doria, F.; Porta, A.; Freccero, M. *J. Org. Chem.* **2011**, *76*, 2319−2323.
(45) Cometti, G.; Du vosel, A.; Francalanci, F.; Santi, R.; Cabri, W.; Foà, M. *J. Organomet. Chem.* **1993**, *451*, C13−C14.