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Palladium-Catalyzed C(sp³)–C(sp²) Cross-Couplings of *O*-(α-Bromoacyl) Cyanohydrins with Boronic Acids: An Entry to Enantioenriched *N*-Acylated β-Amino Alcohols

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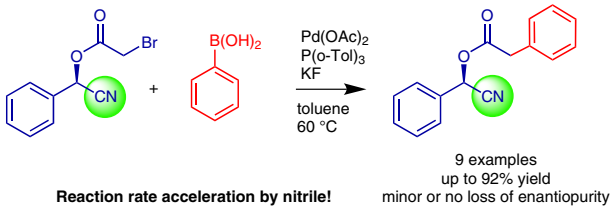
To the memory of Jean Normant for his contributions to organic synthesis



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Abstract Suzuki-type cross-coupling of enantiomerically enriched *O*-(α-bromoacyl) cyanohydrins with aromatic boronic acids substituted with electron-withdrawing or electron-donating groups gave the expected coupling products in high yields without racemization. These substrates exhibit higher reactivities than analogous substrates lacking the nitrile function, probably as a result of π-coordination of the nitrile to palladium. Reduction of the nitrile group of the products, with accompanying intramolecular acyl transfer, provides access to biologically interesting *N*-acylated β-amino alcohols.

Key words Suzuki reactions, cross-coupling, cyanohydrins, amino alcohols, boronic acids, palladium catalysis

O-Acylated cyanohydrins are important intermediates in a range of synthetic transformations and, because of their high stability toward decomposition and racemization, they are more easily handled than the parent cyanohydrins.[1] The acyl group is not only a valuable protecting group, but it also forms a vital part of several interesting compounds. Reduction of the nitrile group to a primary amine with concomitant intramolecular acyl transfer gives the corresponding *N*-substituted β-amino alcohols, many of which show biological activity (Figure 1, a).[2] Because the β-amino alcohol fragment is found in several pharmaceuticals, such as the β_1-adrenoceptor selective agonist denopamine[3] (**1**) and the β_3-adrenoceptor agonist mirabegron[4] (**2**; Figure 1, b), methods that permit ready modification of the structure of the acyl group, thereby providing access to a range of *N*-acylated or *N*-alkylated β-amino alcohols, are attractive. In addition to being valuable intermediates, several *O*-acylated cyanohydrins display biological activity and are used, for example, as insecticides.[5]

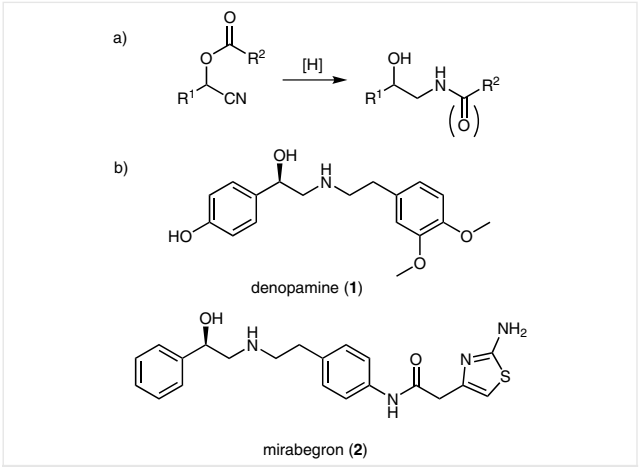


Figure 1 (a) Reduction of *O*-acylated cyanohydrins to *N*-acylated or *N*-alkylated β-amino alcohols. (b) The structures of denopamine (**1**) and mirabegron (**2**).

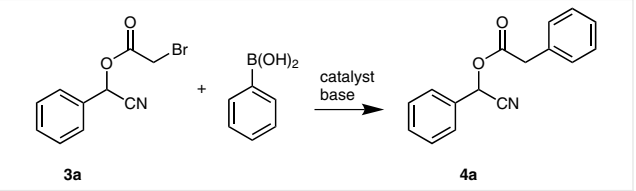
We have developed a method for the synthesis of *O*-acylated cyanohydrins in which a combination of a chiral Lewis acid and a Lewis base catalyzes the reaction of aldehydes with acyl cyanides, usually resulting in high yields of products with high enantiopurity.[6] Alternative ways to access enantioenriched *O*-acylated cyanohydrins rely on acylation of cyanohydrins obtained from other sources of cyanide, such as TMSCN or KCN.[7] A disadvantage of our method and others is that the synthesis of each product requires the use of a specific acyl cyanide or acylating agent. It can be difficult to access these acyl cyanides or acylating agents and, furthermore, some of these compounds display unsatisfactory reactivities or enantioselectivities.[6b,7d]

Starting from a cyanohydrin containing an acyl group with a reactive handle would permit the adoption of a divergent strategy that would avoid the need to optimize the

enantioselective step for each individual acylating agent. We recently showed that *O*-(α-bromoacyl) cyanohydrins react with nitrogen nucleophiles, and that subsequent reduction and intramolecular acyl transfer provide compounds such as the β_3-adrenergic receptor agonist solabegron.[8] The *O*-(α-bromoacyl) cyanohydrins are not accessible by our Lewis acid–Lewis base dual-activation method because of incompatibility between the Lewis base and the required α-bromo-substituted acyl cyanides. However, by employing a minor-enantiomer-recycling strategy that uses a combination of a chiral Lewis acid and a biocatalyst in a two-phase solvent mixture,[9] *O*-(α-bromoacyl) cyanohydrins can be obtained with very high enantiopurities.[10]

To produce further variations in the structure of the acyl chain of the *O*-(α-bromoacyl) cyanohydrins and thereby provide access to other types of products, we considered C–C cross-couplings at the α-position as a highly attractive option. Several strategies have been reported that involve $C(sp^3)$–$C(sp^2)$ couplings with α-halocarbonyl compounds. For example, zinc enolates obtained by treatment of α-bromocarbonyl compounds with metallic zinc can undergo palladium-catalyzed coupling reactions with aryl bromides.[11] In addition, there are reports on the use of Grignard reagents in Kumada cross-coupling reactions.[12] The cross-coupling of an α-bromo ester and an organoboron derivative has been previously reported by Suzuki and co-workers.[13] This transformation was accomplished by using a system consisting of $Pd(PPh_3)_4$ and Tl_2CO_3. Gooßen further developed the reaction and demonstrated its synthetic utility by coupling several boronic acids or pinacol boronates with α-bromo esters and amides.[14] Since then, several examples of cross-coupling reactions of organoboron derivatives with α-halo-substituted esters, amides, or ketones have been reported.[15] Lei and co-workers used $Ni(PPh_3)_4$ as a catalyst for this transformation and were able to couple secondary α-halocarbonyl compounds with boronic acids in good yields.[15d] When a palladium catalyst was used with the same substrate, the homocoupled product was mainly produced. In addition, organotrifluoroborate salts have been successfully coupled with several α-chloro esters or amides.[15i] The method was recently employed in syntheses of several enantioenriched natural products.[16] However, the examples reported to date use α-halo carbonyl compounds that do not contain stereocenters prone to racemization. *O*-(α-Bromoacyl) cyanohydrins were assumed to be particularly challenging substrates because of their labile ester bond, as well as their propensity to undergo racemization in the presence of a base. We therefore expected that milder reaction conditions than those previously employed would be needed to achieve successful coupling.

For our optimization study, we used phenylboronic acid and the *O*-(α-bromoacyl) cyanohydrin **3a**, prepared with high enantiomeric purity by using our minor-enantiomer-recycling method.[10] (Scheme 1). The conditions most often used for cross-couplings of α-halocarbonyl compounds with boronic acid derivatives involve the use of THF or toluene as the solvent; K_2CO_3, Cs_2CO_3, K_3PO_4, or KF as base; and either a palladium or a nickel catalyst in combination with a phosphine ligand. We assumed that carbonate and phosphate bases would be unsuitable in our system because of the risk of racemization, and we therefore selected KF as the base. Our initial attempts employing previously reported conditions with KF as base and THF as solvent, together with $Pd(OAc)_2$ and $(o\text{-Tol})_3P$, at room temperature,[14] gave only the starting material and some degradation products; heating the mixture at 60 °C resulted in increased degradation. Fortunately, by replacing the THF with toluene and heating the mixture at 60 °C, full conversion was observed within 30 minutes, and only minor amounts (<10%) of the protodehalogenated compound were observed. At room temperature, the reaction was sluggish and required approximately two days to reach full conversion.



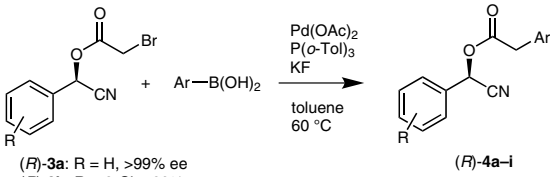
3a 4a

Scheme 1 Cross-coupling of the *O*-(α-bromoacyl) cyanohydrin **3a** with phenylboronic acid

We were pleased to find that a range of boronic acids underwent cross-coupling with enantiopure *O*-(α-bromoacyl) cyanohydrins under our optimized conditions (Table 1). The system tolerated 2-, 3-, or 4-substituted phenylboronic acids with various electronic properties and it gave the desired compounds in high yields with no loss or only minor loss of enantiopurity. Likewise, the *O*-(α-bromoacyl) cyanohydrin obtained from 3-chlorobenzaldehyde[8] coupled with phenylboronic acid to give product **4i** in high yield with only a minor decrease in the ee (Table 1, entry 9); product **4i** is of particular interest, because several *N*-alkylated β-amino alcohols containing a chlorine atom in the 3-position of the aromatic ring show biological activity.[17] Remarkably, the cross-couplings generally proceeded rapidly and reached a full conversion within 30–90 minutes. In contrast, the reaction with (3,4-dimethoxyphenyl)boronic acid was very sluggish and the reaction mixture initially turned into a thick suspension; however, after 24 hours, compound **4g** was isolated in acceptable yield with only minor racemization (Table 1, entry 7).

Unfortunately, we discovered that certain boronic acids containing electron-withdrawing groups were unreactive in our system. [4-(Ethoxycarbonyl)phenyl]boronic acid gave a low conversion, even after 20 hours at 60 °C. However, replacement of $Pd(OAc)_2$ with $Pd_2(dba)_3{\cdot}CHCl_3$ resulted

Table 1 Substrate Scope[a]



(*R*)-**3a**: R = H, >99% ee
(*R*)-**3b**: R = 3-Cl, >99% ee

(*R*)-**4a–i**

Entry	Product	R	Ar	Yield[b] (%)	ee (%)
1	**4a**	H	Ph	89	>99
2	**4b**	H	4-$MeOC_6H_4$	90	>99
3	**4c**	H	2-Tol	90	>99
4	**4d**	H	4-$F_3CC_6H_4$	83	99
5	**4e**	H	1-naphthyl	92	99
6	**4f**	H	3-ClC_6H_4	73	99
7	**4g**	H	3,4-$(MeO)_2C_6H_4$	66	95
8[b]	**4h**	H	4-$EtO_2CC_6H_4$	91	99
9	**4i**	3-Cl	Ph	87	96

[a] Reaction conditions: boronic acid (1.5 equiv), $Pd(OAc)_2$ (3 mol%), (*o*-Tol)$_3$P (9 mol%), KF (3 equiv), toluene, 60 °C.
[b] Isolated yield.

in full conversion after 23 hours at 60 °C, and the desired product **4h** could be isolated in high yield and with high ee (Table 1, entry 8). (4-Cyanophenyl)boronic acid did not give any product under the optimized conditions with $Pd(OAc)_2$ as a source of palladium, but the use of $Pd_2(dba)_3{\cdot}CHCl_3$ resulted in the formation of the product, albeit with low conversion (a 1:1.1 ratio between the starting material and product, according to ^{1}H NMR spectroscopy, after 24 hours at 100 °C). It has been suggested[14] that the boronic acids might act by reducing Pd^{II} to Pd^0; a possible explanation for our results is that this reduction is inefficient with less-nucleophilic boronic acids, and that the use of a Pd^0 precatalyst is required.

The *O*-(α-bromoacyl) cyanohydrin **5** (Figure 2),[10] containing an acyl group with a secondary bromide, did not provide the desired product in the reaction with phenylboronic acid under our optimized conditions or when we used the $Ni(PPh_3)_4$ catalyst system previously used for secondary α-halocarbonyl compounds.[15d]

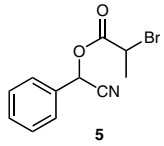
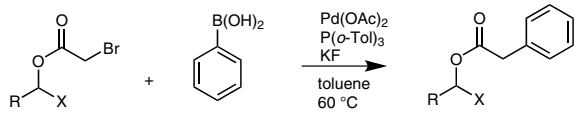


Figure 2 *O*-(α-Bromoacyl) cyanohydrin **5**

To investigate whether the high reaction rates that we observed were due to the presence of the cyano group in the substrates, we treated compound **6** (in which the cyano group was replaced by a methyl group) with phenylboronic acid under our optimized conditions (Scheme 2). When we compared the cross-coupling reaction of **6** with that of **3a**, we found that **4a** was formed at a much higher rate than **7** (Figure 3). To exclude any effect arising from the different steric properties of the nitrile and methyl groups, ethyl bromoacetate (**8**) was subjected to the same reaction conditions. Compound **9** formed with essentially the same low reaction rate as that observed for **7** and, in both cases, large amounts of unreacted substrate remained even after several hours. We assume that side reactions prevail at the concentration used (25 mM) with substrates **6** and **8**, and that either the boronic acid is consumed or the catalyst is destroyed. At the concentration used in the preparative reactions (0.1 M), both substrates reached higher conversions, and higher concentrations of **7** and **9** were obtained.



3a: R = Ph, X = CN
6: R = Ph, X = Me
8: R = Me, X = H

4a: R = Ph, X = CN
7: R = Ph, X = Me
9: R = Me, X = H

Scheme 2 Comparison of reaction rates

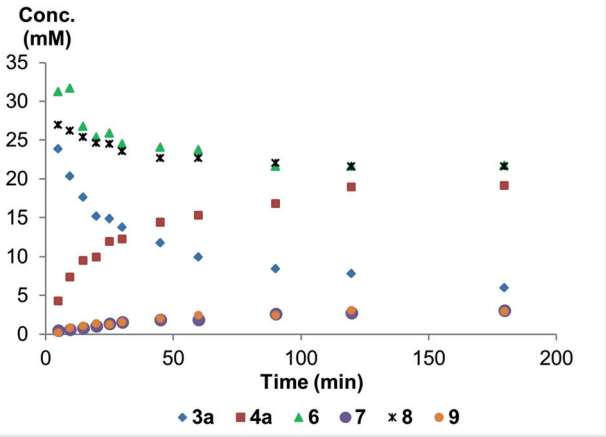
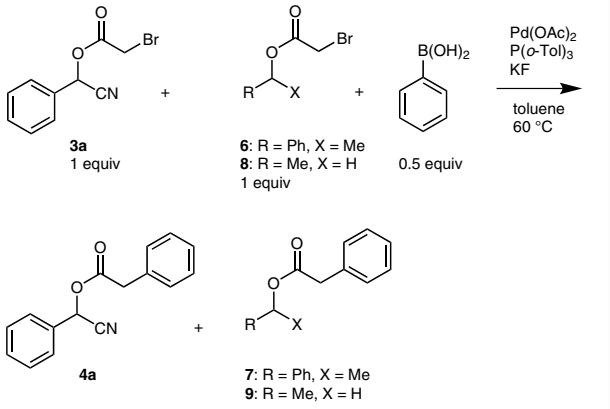


Figure 3 Graph showing concentrations of substrates and products over time. Concentrations were determined by ^{1}H NMR spectroscopic analysis of aliquots taken from the reaction mixtures.

Competition experiments were also performed, in which one equivalent each of **3a** and either **6** or **8** were allowed to compete for 0.5 equivalents of phenylboronic acid under our optimized conditions, and the ratios of the products were determined by ^{1}H NMR spectroscopy (Scheme 3). The ratios between **4a** and either **7** or **9** were essentially equal (~9:1) in both reactions, again confirming that the presence of a nitrile function in **3a** accelerates the cross-coupling reaction.



Scheme 3 Competition experiments

The increased reactivity is suggested to be due to acceleration of the transmetalation, which is usually the slow step in the Suzuki reactions;[18] the acceleration is probably caused by intramolecular π-coordination of the nitrile to palladium. The stabilities of the *cis* and the *trans* palladium complexes of **3a** with internal coordination were calculated by the density functional theory method at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level of theory, including the polarizable conductor calculation model (toluene, UFF) and Grimme dispersion (GD3) (Figure 4). The *trans* complex was found to be 3.7 kcal·mol^{-1} more stable than the *cis* complex (see the Supporting Information). Precedents for this type of π-coordination can be found in reports on several C–H activations in which nitriles were used as *ortho*-directing groups.[19] Additionally, in the palladium-catalyzed hydroarylation of alkynes with boronic acids, the presence of a nitrile function in the substrate led to both an increased yield and a higher regioselectivity; this is believed to be a result of π-coordination of the nitrile during the addition.[20]

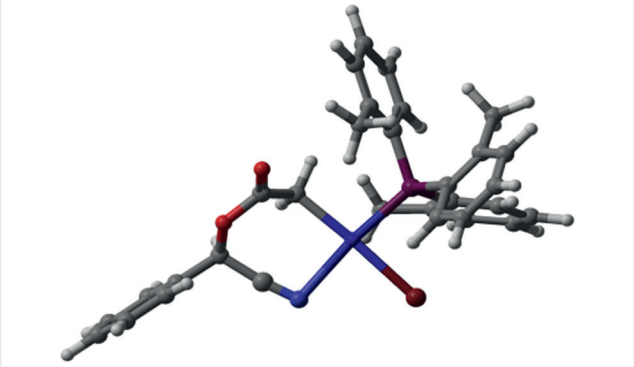
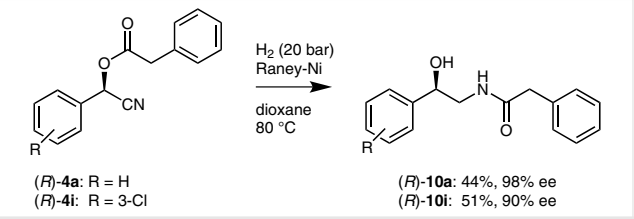


Figure 4 Calculated structure of the palladium–(*o*-Tol)$_3$P complex formed by oxidative addition of **3a** with the coordinated nitrile (Pd, blue; P, violet; O, red; N, light blue; Br, brown).

The synthetic versatility of compounds **4a** and **4i** obtained from the cross-coupling reactions was demonstrated by reduction of the nitrile group by catalytic hydrogenation to give the corresponding *N*-acylated β-amino alcohols **10a** and **10i**. By using the previously optimized conditions,[8] the desired products were obtained with only slight racemization, albeit in moderate yields (Scheme 4).



Scheme 4 Catalytic hydrogenations of nitriles **4a** and **4i**

In conclusion, we have developed a highly efficient protocol for coupling *O*-(α-bromoacyl) cyanohydrins with a range of different boronic acids by using a palladium catalyst. In most cases, the reactions gave high yields of the desired products with only minor loss of enantiomeric purity. Comparison of the reaction rates with those for substrates lacking a nitrile function revealed that the presence of the nitrile group dramatically accelerated the reaction. We also showed that the products obtained could undergo reduction followed by intramolecular acyl transfer to give the corresponding *N*-acylated β-amino alcohols.

All compounds were obtained from commercial suppliers unless stated otherwise. Dry toluene was taken from a Glass Contour solvent-dispensing system, and 1,4-dioxane was distilled over $LiAlH_4$ before use. **CAUTION: KCN is highly toxic and should be handled with great care.** IR spectra were recorded on a Thermo Scientific Nicolet iS10 spectrophotometer. High-resolution mass spectra were recorded on an Orbitrap spectrometer operated in the ESI mode. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DMX 500 and Bruker Ascend 400 spectrometers at 500 or 400 MHz and 125 or 100 MHz, respectively. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to residual $CHCl_3$ in $CDCl_3$. HPLC analyses were conducted on a Shimadzu SIL-20A instrument with a UV detector and a Daicel Chiralpak IC (0.46 cm × 25 cm) or Daicel Chiralcel OD-H (0.46 cm × 25 cm) chiral column. $[\alpha]_D$ values are given in deg·mL·g^{-1}·dm^{-1}.

Cyano(aryl)methyl Arylacetates 4; General Procedure

The appropriate arylboronic acid (1.5 equiv), $Pd(OAc)_2$ (3 mol%), (*o*-Tol)$_3$P (9 mol%), and KF (3 equiv) were added to a flame-dried vial, which was then capped and placed under a N_2 atmosphere. A solution of cyano(aryl)methyl bromoacetate **3a**[10] or **3b**[8] (1 equiv) in toluene was added to the vial from a syringe, and the resulting mixture was stirred at 60 °C for the indicated time. The mixture was filtered through Celite and eluted with EtOAc. The solvents were evaporated and the crude product was purified by flash chromatography.

(*R*)-Cyano(phenyl)methyl Phenylacetate (4a)

The general procedure was followed starting from **3a** (101 mg, 0.398 mmol), PhB(OH) (72.7 mg, 0.596 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol), (*o*-Tol)$_3$P (10.9 mg, 0.036 mmol), and KF (69.3 mg, 1.19 mmol)

in toluene (4 mL) for 30 min. Flash chromatography [silica gel, CH_2Cl_2–PE (2:1)] gave a colorless oil; yield: 88.8 mg (0.353 mmol, 89%; >99% ee); R_f = 0.55; $[\alpha]_D^{25}$ –0.37 (*c* 2.2, CH_2Cl_2).[21]

HPLC [Daicel Chiralcel OD-H, hexanes–*i*-PrOH (95:5, 1 mL/min), λ = 220 nm]: t_R (major): 12.3 min; t_R (minor): 17.9 min.

IR (neat): 3065, 3033, 2946, 1751, 1497, 1456, 1129 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.48 (m, 5 H), 7.28–7.35 (m, 3 H), 7.24–7.27 (m, 2 H), 6.43 (s, 1 H), 3.75 (A part of AB, *J* = 15.5 Hz, 1 H), 3.71 (B part of AB, *J* = 15.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 132.6, 131.8, 130.5, 129.4, 128.9, 127.9, 127.7, 116.1, 63.3, 40.8.

HRMS (ESI-Orbitrap): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{13}NNaO_2$: 274.0838; found: 274.0834.

(*R*)-Cyano(phenyl)methyl (4-Methoxyphenyl)acetate (4b)

The general procedure was followed starting from **3a** (99.2 mg, 0.390 mmol), (4-methoxyphenyl)boronic acid (89.0 mg, 0.586 mmol), $Pd(OAc)_2$ (2.6 mg, 0.012 mmol), (*o*-Tol)$_3$P (10.7 mg, 0.035 mmol), and KF (68.0 mg, 1.17 mmol) in toluene (4 mL) for 30 min. Flash chromatography [silica gel, CH_2Cl_2–PE (3:1)] gave a colorless oil; yield: 99.1 mg (0.352 mmol, 90%; >99% ee); R_f = 0.33; $[\alpha]_D^{24}$ –1.3 (*c* 2.1, CH_2Cl_2).[21]

HPLC [Daicel Chiralcel OD-H, hexanes–i-PrOH (95:5, 1 mL/min), λ = 220 nm]: t_R (major): 17.7 min; t_R (minor): 25.4 min.

IR (neat): 3036, 2935, 2837, 1750, 1514, 1250, 1128 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.49 (m, 5 H), 7.17 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 6.42 (s, 1 H), 3.80 (s, 3 H), 3.68 (A part of AB, *J* = 15.6 Hz, 1 H), 3.65 (B part of AB, *J* = 15.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 159.2, 131.9, 130.52, 130.46, 129.4, 127.9, 124.6, 116.2, 114.3, 63.2, 55.4, 39.9.

HRMS (ESI-Orbitrap): *m/z* $[M + H]^+$ calcd for $C_{17}H_{16}NO_3$: 282.1125; found: 282.1118.

(*R*)-Cyano(phenyl)methyl (2-Tolyl)acetate (4c)

The general procedure was followed starting from **3a** (103 mg, 0.405 mmol), (2-tolyl)boronic acid (82.7 mg, 0.608 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol), (*o*-Tol)$_3$P (11.1 mg, 0.036 mmol), and KF (70.7 mg, 1.22 mmol) in toluene (4 mL) for 30 min. Flash chromatography [silica gel, CH_2Cl_2–PE (2:1)] gave a pale-yellow solid; yield: 96.8 mg (0.365 mmol, 90%; >99% ee); mp 76–78 °C; R_f = 0.53; $[\alpha]_D^{26}$ –3.9 (*c* 2.2, CH_2Cl_2).

HPLC [Daicel Chiralcel OD-H, hexanes–i-PrOH (95:5), 1 mL/min; λ = 220 nm]: t_R (major): 13.2 min; t_R (minor): 18.8 min.

IR (neat): 2958, 2916, 1761, 1124 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.48 (m, 5 H), 7.15–7.23 (m, 4 H), 6.43 (s, 1 H), 3.75 (A part of AB, *J* = 16.0 Hz, 1 H), 3.72 (B part of AB, *J* = 16.0 Hz, 1 H), 2.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 137.0, 131.8, 131.4, 130.7, 130.5, 130.3, 129.4, 128.0, 127.9, 126.5, 116.1, 63.3, 38.7, 19.7.

HRMS (ESI-Orbitrap): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{15}NNaO_2$: 288.0995; found: 288.0984.

(*R*)-Cyano(phenyl)methyl [4-(Trifluoromethyl)phenyl]acetate (4d)

The general procedure was followed starting from **3a** (103 mg, 0.405 mmol), [4-(trifluoromethyl)phenyl]boronic acid (115 mg, 0.605 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol), (*o*-Tol)$_3$P (11.1 mg, 0.036 mmol), and KF (70.5 mg, 1.21 mmol) in toluene (4 mL) for 30 min. Flash chromatography [silica gel, CH_2Cl_2–PE (1:1)] gave a white solid; yield: 107 mg (0.336 mmol, 83%; 99% ee); mp 60–61 °C; R_f = 0.41; $[\alpha]_D^{26}$ –2.6 (*c* 1.8, CH_2Cl_2).

HPLC [Daicel Chiralcel OD-H, hexanes–i-PrOH (95:5), 1 mL/min; λ = 220 nm]: t_R (major): 15.9 min; t_R (minor): 19.7 min.

IR (neat): 2953, 1751, 1332, 1146, 1120 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.0 Hz, 2 H), 7.42–7.50 (m, 5 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 6.43 (s, 1 H), 3.81 (A part of AB, *J* = 15.8 Hz, 1 H), 3.77 (B part of AB, *J* = 15.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 136.5 (q, J_{C-F} = 1.1 Hz), 131.6, 130.7, 130.2 (q, J_{C-F} = 32.7 Hz), 129.8, 129.5, 128.0, 125.9 (q, J_{C-F} = 3.8 Hz), 124.1 (q, J_{C-F} = 272.1 Hz), 115.9, 63.6, 40.4.

HRMS (ESI-Orbitrap): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{12}F_3NNaO_2$: 342.0712; found: 342.0703.

(*R*)-Cyano(phenyl)methyl (1-Naphthyl)acetate (4e)

The general procedure was followed starting from **3a** (100 mg, 0.395 mmol), 1-naphthylboronic acid (102 mg, 0.593 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol), (*o*-Tol)$_3$P (10.8 mg, 0.035 mmol), and KF (68.9 mg, 1.19 mmol) in toluene (4 mL) for 30 min. Flash chromatography [silica gel, CH_2Cl_2–PE (2:1)] gave a colorless gum; yield: 109 mg (0.362 mmol, 92%; 99% ee); R_f = 0.54; $[\alpha]_D^{26}$ –12.1 (*c* 2.7, CH_2Cl_2).

HPLC [Daicel Chiralcel OD-H, hexanes–i-PrOH (95:5), 1 mL/min; λ = 254 nm]: t_R (major): 23.5 min; t_R (minor): 42.5 min.

IR (neat): 3064, 2947, 1751, 1128 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.90 (m, 3 H), 7.47–7.52 (m, 2 H), 7.36–7.45 (m, 7 H), 6.44 (s, 1 H), 4.19 (A part of AB, *J* = 16.0 Hz, 1 H), 4.16 (B part of AB, *J* = 16.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 134.0, 132.0, 131.8, 130.5, 129.3, 129.2, 129.0, 128.7, 128.3, 127.9, 126.8, 126.1, 125.6, 123.5, 116.1, 63.4, 38.6.

HRMS (ESI-Orbitrap): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{15}NNaO_2$: 324.0995; found: 324.0984.

(*R*)-Cyano(phenyl)methyl (3-Chlorophenyl)acetate (4f)

The general procedure was followed starting from **3a** (102 mg, 0.401 mmol), (3-chlorophenyl)boronic acid (94.1 mg, 0.602 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol), (*o*-Tol)$_3$P (11.0 mg, 0.036 mmol), and KF (69.9 mg, 1.20 mmol) in toluene (4 mL) for 90 min. Flash chromatography [silica gel, CH_2Cl_2–PE (1:1)] gave a pale-yellow solid; yield: 83.8 mg (0.293 mmol, 73%; 99% ee); mp 41–43 °C; R_f = 0.35; $[\alpha]_D^{25}$ –3.2 (*c* 1.9, CH_2Cl_2).

HPLC [Daicel Chiralcel OD-H, hexanes–i-PrOH (95:5), 1 mL/min; λ = 220 nm]: t_R (major): 15.1 min; t_R (minor): 21.5 min.

IR (neat): 2941, 1753, 1134 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.50 (m, 5 H), 7.24–7.30 (m, 3 H, overlapped with $CHCl_3$), 7.12–7.16 (m, 1 H), 6.43 (s, 1 H), 3.72 (A part of AB, *J* = 15.7 Hz, 1 H), 3.69 (B part of AB, *J* = 15.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 134.7, 134.4, 131.6, 130.7, 130.1, 129.6, 129.5, 128.02, 127.98, 127.6, 116.0, 63.5, 40.3.

HRMS (ESI-Orbitrap): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{12}ClNNaO_2$: 308.0449; found: 308.0438.

(*R*)-Cyano(phenyl)methyl (3,4-Dimethoxyphenyl)acetate (4g)

The general procedure was followed starting from **3a** (107 mg, 0.421 mmol), (3,4-dimethoxyphenyl)boronic acid (115 mg, 0.632 mmol), $Pd(OAc)_2$ (2.8 mg, 0.012 mmol), (*o*-Tol)$_3$P (11.5 mg, 0.038 mmol), and

KF (73.4 mg, 1.26 mmol) in toluene (4.2 mL) for 24 h. Flash chromatography [silica gel, PE–EtOAc (4:1)] gave a pale-yellow oil; yield: 86.1 mg (0.277 mmol, 66%; 95% ee); R_f = 0.29; $[\alpha]_D^{26}$ –0.90 (*c* 2.2, CH_2Cl_2).

HPLC [Daicel Chiralcel OD-H, hexanes–i-PrOH (95:5), 1 mL/min; λ = 254 nm]: t_R (major): 41.1 min; t_R (minor): 51.4 min.

IR (neat): 3002, 2936, 2836, 1751, 1516, 1264, 1239, 1129, 1027 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.50 (m, 5 H), 6.75–6.84 (m, 3 H), 6.43 (s, 1 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 3.68 (A part of AB, *J* = 15.4 Hz, 1 H), 3.65 (B part of AB, *J* = 15.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 149.2, 148.7, 131.8, 130.6, 129.4, 127.9, 125.0, 121.7, 116.1, 112.3, 111.5, 63.3, 56.1, 56.0, 40.4.

HRMS (ESI-Orbitrap): *m/z* [M + H]$^+$ calcd for $C_{18}H_{18}NO_4$: 312.1230; found: 312.1229.

(*R*)-(3-Chlorophenyl)(cyano)methyl Phenylacetate (4i)

The general procedure was followed starting from **3b** (119 mg, 0.412 mmol), PhB(OH) (75.4 mg, 0.618 mmol), $Pd(OAc)_2$ (2.8 mg, 0.012 mmol), (*o*-Tol)$_3$P (11.3 mg, 0.037 mmol), and KF (71.8 mg, 1.24 mmol) in toluene (4 mL) for 30 min. Flash chromatography [silica gel, CH_2Cl_2–PE (2:1)] gave a colorless oil; yield: 103 mg (0.360 mmol, 87%; 96% ee); R_f = 0.56; $[\alpha]_D^{24}$ –1.2 (*c* 2.0, CH_2Cl_2).

HPLC [Daicel Chiralcel OD-H, hexanes–i-PrOH (95:5), 1 mL/min; λ = 220 nm]: t_R (major): 14.3 min; t_R (minor): 21.5 min.

IR (neat): 3065, 3032, 2944, 1755, 1128 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.45 (m, 2 H), 7.31–7.39 (m, 5 H), 7.25–7.28 (m, 2 H, overlapped with $CHCl_3$), 6.39 (s, 1 H), 3.76 (A part of AB, *J* = 15.5 Hz, 1 H), 3.73 (B part of AB, *J* = 15.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 135.4, 133.6, 132.4, 130.8, 130.7, 129.4, 129.0, 127.92, 127.85, 125.9, 115.6, 62.5, 40.7.

HRMS (ESI-Orbitrap): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{12}ClNNaO_2$: 308.0449; found: 308.0443.

Ethyl 4-{2-[(*R*)-Cyano(phenyl)methoxy]-2-oxoethyl}benzoate (4h)

A flame-dried vial was charged with [4-(ethoxycarbonyl)phenyl]boronic acid[22] (123 mg, 0.634 mmol), (*o*-Tol)$_3$P (11.6 mg, 0.038 mmol), and KF (73.6 mg, 1.27 mmol), then moved to a glovebox under a N_2 atmosphere. $Pd_2(dba)_3$·$CHCl_3$ (6.6 mg, 0.0064 mmol) was added to the vial, which was then capped and removed from the glovebox. A solution of **3a** (107 mg, 0.422 mmol) in toluene (4.2 mL) was added from a syringe and the resulting mixture was stirred at 60 °C for 23 h. The mixture was then filtered over Celite and eluted with EtOAc. The solvents were evaporated, and the resulting residue was purified by flash chromatography [silica gel, CH_2Cl_2–PE (9:1)] to give a pale-yellow oil; yield: 125 mg (0.386 mmol, 91%; 99% ee); R_f = 0.19; $[\alpha]_D^{25}$ –2.2 (*c* 2.0, CH_2Cl_2).

HPLC [Daicel Chiralcel OD-H, hexanes–i-PrOH (95:5), 1 mL/min; λ = 220 nm]: t_R (major): 22.4 min; t_R (minor): 27.5 min.

IR (neat): 2924, 1754, 1716, 1278, 1128, 1107 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.2 Hz, 2 H), 7.41–7.50 (m, 5 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 6.43 (s, 1 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 3.80 (A part of AB, *J* = 15.7 Hz, 1 H), 3.77 (B part of AB, *J* = 15.7 Hz, 1 H), 1.39 (t_R, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 166.4, 137.5, 131.6, 130.7, 130.2, 130.1, 129.443, 129.437, 128.0, 116.0, 63.5, 61.2, 40.7, 14.5.

HRMS (ESI-Orbitrap): *m/z* [M + H]$^+$ calcd for $C_{19}H_{18}NO_4$: 324.1230; found: 324.1230.

(*rac*)-Cyano(phenyl)methyl Bromoacetate (3a)[10]

Sodium bisulfite (a mixture of $NaHSO_3$ and $Na_2S_2O_5$) (3.8 g) was dissolved in H_2O (10 mL) and the solution was cooled to 0 °C. PhCHO (1.0 mL, 9.84 mmol) was added, and the solution was stirred at 0 °C for 30 min. A solution of KCN (2.6 g, 39.9 mmol) (**CAUTION!**) in H_2O (50 mL) was added dropwise, and the resulting mixture was stirred at r.t. for 2.5 h, then extracted with Et_2O The combined organic fractions were washed successively with brine and 0.1 M aq HCl, then dried (Na_2SO_4) and concentrated. The resulting residue and pyridine (1.0 mL, 12.4 mmol) were dissolved in CH_2Cl_2 (30 mL), and the solution was cooled to 0 °C. $BrCH_2COBr$ (1.1 mL, 12.6 mmol) was added dropwise, and the solution was stirred at r.t. for 1 h. Sat. aq NH_4Cl was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by flash chromatography [silica gel, PE–EtOAc (9:1)] to give a pale-yellow oil; yield: 1.86 g (7.32 mmol, 74%); R_f = 0.32.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.57 (m, 2 H), 7.45–7.51 (m, 3 H), 6.45 (s, 1 H), 3.92 (A part of AB, *J* = 12.7 Hz, 1 H), 3.90 (B part of AB, *J* = 12.7 Hz, 1 H).

1-Phenylethyl Bromoacetate (6)[23]

1-Phenylethanol (0.50 mL, 4.1 mmol) and pyridine (0.67 mL, 8.3 mmol) were dissolved in CH_2Cl_2 (30 mL). The resulting solution was cooled to 0 °C, and $BrCH_2COBr$ (0.72 mL, 8.3 mmol) was added dropwise. The mixture was stirred at r.t. for 2 h and then sat. aq NH_4Cl was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic fractions were washed once with sat. aq $CuSO_4$ then dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography [silica gel, PE–EtOAc (19:1)] to give a colorless oil; yield: 889 mg (3.66 mmol, 88%); R_f = 0.42.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.39 (m, 5 H), 5.93 (q, *J* = 6.6 Hz, 1 H), 3.84 (s, 2 H), 1.59 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 140.8, 128.7, 128.4, 126.3, 74.6, 26.3, 22.1.

Reaction Rate Measurements; General Procedure

A flame-dried vial was charged with PhB(OH)$_2$ (0.15 mmol), $Pd(OAc)_2$ (0.006 mmol), (*o*-Tol)$_3$P (0.018 mmol), and KF (0.6 mmol) then capped and placed under a N_2 atmosphere. A solution of the substrate (**3a**, **6**, or **8**; 0.1 mmol) and 1-methoxynaphthalene (5 µL, 0.034 mmol) in toluene (4 mL) was added to the vial from a syringe, and the resulting mixture was stirred at 60 °C. The concentrations of substrates and products were determined by transferring aliquots of the solutions with a syringe directly into NMR tubes containing $CDCl_3$ for analysis by ^1H NMR. The spectral data for **7**[24] and **9**[15h] were identical to the published values.

Competition Experiments; General Procedure

A flame-dried vial was charged with PhB(OH)$_2$ (0.1 mmol), $Pd(OAc)_2$ (0.003 mmol), (*o*-Tol)$_3$P (0.009 mmol), and KF (0.3 mmol), then capped and placed under a N_2 atmosphere. A solution of **3a** (0.2 mmol) and either **6** or **8** (0.2 mmol) in toluene (2 mL) was added to the vial from a syringe, and the resulting mixture was stirred at 60 °C. After 6 h, an aliquot of the reaction mixture was removed by using a syringe and analyzed by ^1H NMR.

Hydrogenation Reactions; General Procedure

Raney nickel (4200; aqueous slurry) was activated before use by treatment with 0.1 M aq NaOH, washing with H_2O to a neutral pH, and finally washing with MeOH (×2).

A solution of the substrate in 1,4-dioxane was added to the activated catalyst in an autoclave, which was sealed and flushed once with H_2 before increasing the pressure to 20 bar. The mixture was stirred at 80 °C for 3 h, cooled to r.t., filtered over Celite with EtOAc as eluent, and concentrated. The residue was purified by flash chromatography.

***N*-[(2*R*)-2-Hydroxy-2-phenylethyl]-2-phenylacetamide (10a)**

The general procedure was followed starting from **4a** (73.4 mg, 0.292 mmol) with Raney nickel (129 mg) in 1,4-dioxane (2.2 mL). Flash chromatography [silica gel, PE–EtOAc (1:2)] gave a pale-yellow solid; yield: 32.7 mg (0.128 mmol, 44%; 98% ee); R_f = 0.32; $[\alpha]_D^{26}$ –52.5 (*c* 0.83, CH_2Cl_2).

HPLC [Daicel Chiralpak IC, hexanes–i-PrOH (90:10), 0.7 mL/min; λ = 220 nm]: t_R (major): 50.9 min; t_R (minor): 63.2 min.

IR (neat): 3291, 3029, 2918, 1656, 1545, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.36 (m, 8 H), 7.21 (d, *J* = 7.1 Hz, 2 H), 5.77 (br s, 1 H), 4.80 (dd, *J* = 3.4, 7.4 Hz, 1 H), 3.64 (ddd, *J* = 3.4, 6.6, 14.1 Hz, 1 H), 3.58 (s, 2 H), 3.33 (ddd, *J* = 5.7, 7.7, 13.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7, 141.7, 134.6, 129.6, 129.2, 128.7, 128.0, 127.6, 125.9, 73.8, 47.7, 43.8.

HRMS (ESI-Orbitrap): *m/z* $[M + H]^+$ calcd for $C_{16}H_{18}NO_2$: 256.1332; found: 256.1324.

***N*-[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-2-phenylacetamide (10i)**

The general procedure was followed starting from **4i** (61.9 mg, 0.217 mmol) with Raney nickel (95 mg) in 1,4-dioxane (3.4 mL). Flash chromatography [silica gel, PE–EtOAc (1:3)] gave a colorless gum; yield: 31.9 mg (0.110 mmol, 51%; 90% ee); R_f = 0.37; $[\alpha]_D^{26}$ –43.5 (*c* 2.0, CH_2Cl_2).

HPLC [Daicel Chiralpak IC, hexanes–i-PrOH (90:10), 0.7 mL/min; λ = 220 nm]: t_R (major): 26.5 min; t_R (minor): 33.8 min.

IR (neat): 3307, 3064, 3030, 2927, 1646, 1539 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.37 (m, 4 H), 7.18–7.25 (m, 4 H), 7.12–7.15 (m, 1 H), 5.74 (br s, 1 H), 4.80 (dd, *J* = 3.2, 7.0 Hz, 1 H), 3.63 (ddd, *J* = 3.3, 6.6, 14.3 Hz, 1 H), 3.58 (s, 2 H), 3.31 (ddd, *J* = 5.8, 6.9, 14.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.2, 143.9, 134.6, 134.4, 129.9, 129.6, 129.3, 128.0, 127.7, 126.2, 124.1, 73.4, 47.8, 43.7.

HRMS (ESI-Orbitrap): *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}ClNO_2$: 290.0942; found: 290.0932.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562445. Results from competition experiments, NMR spectra, HPLC, and computational details are included.

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