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Investigations into the Suzuki–Miyaura coupling aiming at multikilogram synthesis of E2040 using (*o*-cyanophenyl)boronic esters

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Abstract

The Suzuki–Miyaura cross-coupling reaction between 1-{3-bromo-4-chloro-5-[1-(*R*)-fluoropropyl]}phenylpiperazine ((***R***)-**1b**) and thermally unstable (*o*-cyanophenyl)boronic ester **6b** in the presence of dichlorobis(triphenylphosphine)palladium and potassium phosphate hydrate in boiling toluene was found to afford 1-{3-(2-cyanophenyl)-4-chloro-5-[1-(*R*)-fluoropropyl]}phenylpiperazine ((***R***)-**5**), an intermediate for the synthesis of E2040, in excellent yields. The reaction conditions for the cross-coupling were optimized by the design of experiments (DOE) approach and found to be applicable to electron-rich and/or sterically hindered aryl bromides. Safety evaluation for the production of (***R***)-**5** is also described. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Suzuki–Miyaura cross-coupling; E2040; DOE; Reductive debromination; Scale-up

1. Introduction

E2040 is a potent antagonist of $D_3/D_2/5\text{-}HT_2$ receptors being developed for the treatment and amelioration of mental disorders such as aggressive behavior due to senile dementia, mental excitation, poriomania, delirium, hallucination, hyperkinesias, schizophrenia, emotional disturbance, depression, neurosis, psychophysiologic disorder and anxiety [1].

The distinct structural features of E2040 are the presence of a fluorine atom at a chiral center, and a cyano group at the 2′-position of the biphenyl moiety. Initially, E2040 was synthesized according to the synthetic route summarized in Scheme 1. In this scheme, the introduction of cyano group to the 2′-position of the biphenyl moiety was achieved via a formyl precursor (**3**), which was prepared by a cross-coupling reaction of aryl bromide (**1a**) with (*o*-formylphenyl)-boronate (**2**) [2].

The major problems of this route in large-scale synthesis were optical resolution at the final stage, and multi-step sequence (coupling–oximation–dehydration) to form the cyanobiphenyl moiety. We thus decided to focus our attention on finding a more straightforward process via a metal-catalyzed biaryl coupling of optically active (***R***)-**1b** with an appropriate arylmetal (**6**) to obtain (***R***)-**5** (Scheme 2).

Many studies describing the construction of 2-cyanobiphenyl as well as the corresponding carboxylic acid, ester and tetrazoyl derivatives for a large number of active pharmaceutical ingredients (API) employ the Suzuki–Miyaura coupling reaction using 2-bromobenzonitrile as an electrophile [3]. Other methods such as the Stille-type cross-coupling [4], zinc reagents [5] and the Grignard reactions [6] have also been reported. Among them, the Suzuki–Miyaura reaction is a useful cross-coupling method for synthesis of pharmaceutical compounds because of the low toxicity of the reagents, its broad activity, and the ability to conduct the reaction even under aqueous conditions.

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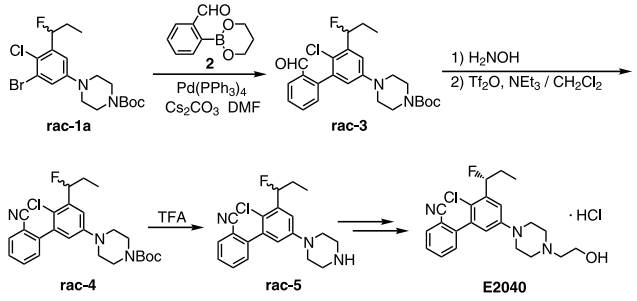
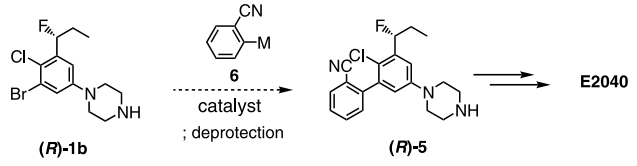
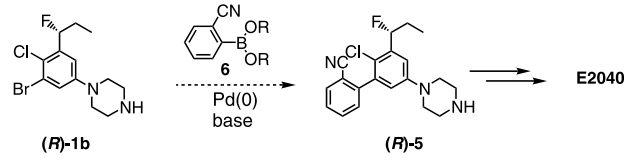
The preparation of the cyanophenyl group as an electrophilic agent requires the generation of an anion followed by transmetallation on the main structural frame, thus its usefulness is limited by the necessity for a protective group. For the synthesis of Losartan, the introduction of phenyltetrazole component is efficiently attained by using 5-(2′-boronophenyl)-2-(triphenylmethyl)-2*H*-tetrazole [7]. Our investigation into the preparation of the cyanobiphenyl moiety by the Suzuki–Miyaura coupling using (*o*-cyanophenyl)-boronic acid (**6a**) led us to the design of a new route for the manufacture of E2040 on a multikilogram scale (Scheme 3).



Scheme 1.



Scheme 2.



Scheme 3.

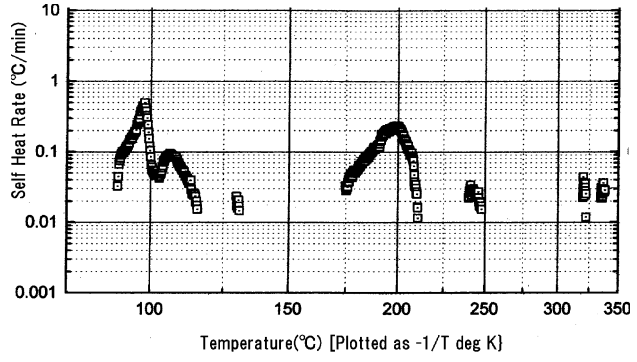


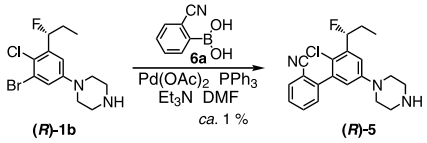
Fig. 1. Heat generating rate vs. temperature plot of **6a**. Measured and analyzed by an ARC.

The potential of this route was dramatically increased by the establishment of an efficient optical resolution method for the biphenyl (***R***)-**5**. We focused our synthetic efforts on cross-coupling reaction between bromide (***R***)-**1b** and (*o*-cyanophenyl)boronate (**6**) as the key reaction for the preparation of (***R***)-**5**.

2. Results and discussion

2.1. Route elucidation

There is only one report [8] that describes the use of (*o*-cyanophenyl)boronic acid (**6a**) (conditions: $Pd(PPh_3)_4$, Et_3N, DMF) for cross-coupling of 4-(4-bromo-2-fluoro-benzyloxy)-2-ethyl-5,6,7,8-tetrahydroquinoline to give the 2-cyanobiphenyl compound in a moderate yield (67%). In our first attempt we synthesized **6a** in ca. 50% yield by halogen–lithium exchange of *o*-bromobenzonitrile followed by trapping of the anion with $B(OMe)_3$ and hydrolysis. We then applied the cross-coupling conditions to (***R***)-**1b** to obtain (***R***)-**5** with a yield of 1% (Eq. (1)).



(1)

Accelerating rate calorimetry (ARC) analysis of (*o*-cyanophenyl)boronic acid (**6a**) showed that it has an exothermic nature when heated at around 90 °C, and that this heat may trigger successive decomposition accompanied by further generation of extreme amounts of heat (Fig. 1).

We presume that when **6a** is heated, the cyano group undergoes hydrolysis caused by the participation of the neighboring –OH group to form the amide biphenyl compound. Cross-coupling of unstable boronic acids in the presence of a fluoride ion has been reported [9], but when (***R***)-**1b** and **6a** were used, both hydrous and anhydrous conditions gave poor results. These were caused by the considerably longer reaction time required under these conditions, which in turn caused decomposition of boronic acid in the presence or absence of water.

Considering that even storage at room temperature caused its decomposition, we concluded that **6a** was not suitable for large-scale synthesis.

We then decided to utilize a boronic acid trimethylene ester (**6b**), as it has been reported that (*o*-formylphenyl)boronic acid is stabilized by transformation into the corresponding boronic ester [10]. Esterification with 1,3-propanediol gave crystalline **6b** quantitatively, which was thermally more stable than **6a** and could be purified by recrystallization (Eq. (2)).

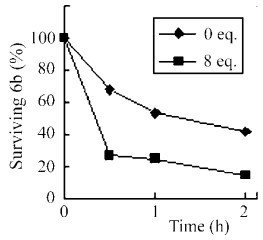
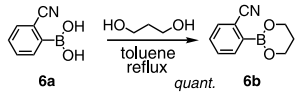
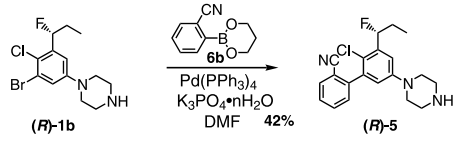


Fig. 2. Stability of **6b** in the reaction conditions in the presence of varied equivalents of water (zero and eight equivalents). Surviving **6b** (%) was calculated by HPLC area of **6b**/initial **6b** HPLC area. Reaction conditions: $PdCl_2(PPh_3)_2$, 1 mol%; K_3PO_4, 1.5 M; toluene, fivefold-volume against **6b**; 100 °C.



(2)

An initial experiment using (***R***)-**1b** and **6b** under ordinary conditions ($Pd(PPh_3)_4$, $K_3PO_4{\cdot}nH_2O$, DMF) gave (***R***)-**5** in a moderate yield (Eq. (3)). This reaction was viable and had scope for becoming a highly efficient method for the synthesis of (***R***)-**5**.



(3)

2.2. Optimization

The most suitable reagents (palladium source, ligand, base, and solvent) and conditions (water content and temperature) for the reaction were optimized with regards to yield, cost, purity, reproducibility for large-scale synthesis, and safety for operation in a pilot plant. At first, we evaluated the initial synthetic route (Scheme 1) with boronate **6b**. The results showed that boronate **6b** were susceptible to decomposition when heated for prolonged periods of time. It also quickly decomposed in the presence of water, as shown in Fig. 2, and even under anhydrous conditions, the amount was reduced by 40% after 2 h.

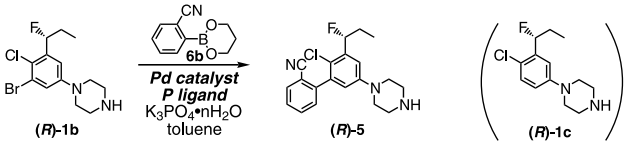
Taking the above into consideration, we recognized that the optimum reaction conditions had to encompass fast consumption of (***R***)-**1b**. For a practical synthesis, it meant that the reaction must be finished within 2 h because of the unstable nature of **6b**.

2.2.1. Pd source and ligand

Among the catalysts, $Pd(PPh_3)_4$ is widely used and commercially available, but not suitable for large-scale synthesis because of its poor stability in air and modest yields in bench-scale synthesis. Other available and inexpensive palladium sources, $PdCl_2$ and $Pd(OAc)_2$ in combination with PPh_3, $PdCl_2(PPh_3)_2$ and Pd–C [11], which has been reported to leave smaller amounts of residual palladium, were evaluated using toluene and $K_3PO_4{\cdot}nH_2O$.

Coupling reactions in the presence of 2 mol% of $PdCl_2$ or $Pd(OAc)_2$ and 8 mol% of PPh_3 consumed completely the substrates within 1 h to afford (***R***)-**5** in more than 76% yield (Table 1).

Table 1
Effect of various catalyst systems on the coupling reaction of (***R***)-**1b** and **6b**



Entry	Catalyst [a]	Ligand	Conversion [b] (%)	Yield of (***R***)-**5** (%)
1	$PdCl_2$	PPh_3 [c]	95	76
2	$Pd(OAc)_2$	PPh_3 [c]	100	92
3	$PdCl_2(PPh_3)_2$	None	100	92
4	Pd–C	None	Trace	–
5	$Pd(OAc)_2$	1,2-Bis(diphenylphosphino)ethane [d]	62	40
6	$Pd(OAc)_2$	1,3-Bis(diphenylphosphino)propane [d]	Trace	–
7	$Pd(OAc)_2$	1,4-Bis(diphenylphosphino)butane [d]	68	42
8	$Pd(OAc)_2$	1,5-Bis(diphenylphosphino)pentane [d]	67	43
9	$Pd(OAc)_2$	1,6-Bis(diphenylphosphino)hexane [d]	67	45
10	$Pd(OAc)_2$	Tri(*o*-tolyl)phosphine [c]	18	8

[a] 2 mol% of Pd were used.
[b] The term 'Conversion' means the ratio ((***R***)-**5**/((***R***)-**5**–(***R***)-**1b**)) calculated from HPLC relative area % of each compound.
[c] 8 mol% of ligands were used.
[d] 4 mol% of ligands were used.

Table 2
Effect of various bases on the coupling reaction of (***R***)-**1b** and **6b** (1.5 M equivalents) [a]

Entry	Base	Conversion [b] (%)
1	$K_3PO_4 \cdot nH_2O$	100
2	K_3PO_4	79
3	$Ba(OH)_2 \cdot 8H_2O$	17
4	KF	70
5	$KF \cdot 2H_2O$	80

[a] $PdCl_2(PPh_3)_2$ was used as a catalyst and toluene as a solvent.
[b] The term 'Conversion' means the ratio ((***R***)-**5**/((***R***)-**5**–(***R***)-**1b**)) calculated from HPLC relative area % of each compound.

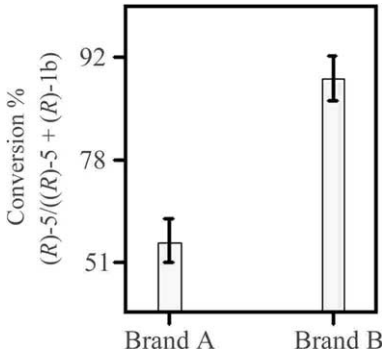


Fig. 3. Difference of particle size and activity between two brands. Yields of the reaction after 30 min. Fifty percent cumulate particle diameter: brand A, 410 μm; brand B 237 μm.

On the other hand, the activity of Pd(0) catalysts, which are generated by combination of inorganic Pd salts with PPh_3, has tendency to decrease with quality of PPh_3 owing, e.g. to air-oxidation leading to inert triphenylphosphine oxide. The heterogeneous catalyst, Pd–C, gave trace amounts of biphenyl (***R***)-**5** even in alcohols that are normally used as a solvent for this type of reaction.

The stable catalyst, $PdCl_2(PPh_3)_2$, also gave a good yield. This catalyst was thought to be optimal, because it is stable in the air and requires no additional ligand.

Some other phosphine compounds were also evaluated as ligands in combination with $Pd(OAc)_2$. However, none of them consumed (***R***)-**1b** completely. We consider that the higher basicity of these ligands increased stability of the phosphine-coordinated palladium and thus, decreased the reaction rate allowing the decomposition of boronate. The ratio of (***R***)-**1c** was greater when $(o\text{-tol})_3P$ was used. High basicity and steric hindrance seemed to accelerate the oxidative addition over transmetallation (Pd → B).

Among all of the catalysts evaluated, $PdCl_2(PPh_3)_2$ was found to be the best.

2.2.2. Base

Next, we examined the effect of several bases on the cross-coupling reaction. $K_3PO_4 \cdot nH_2O$ produced desired product in high yield (Table 2). In contrast, when KF or $KF \cdot 2H_2O$ was used as a base, the substrates were not consumed completely because of the slow rate of the reaction.

The use of anhydrous K_3PO_4 or $K_3PO_4 \cdot nH_2O$ as the base was then considered. As anhydrous K_3PO_4 alone significantly decreased the reaction rate, it was clear that the presence of water was essential to achieve an adequate reaction rate. However, an excess amount of water would cause hydrolysis of the boronate and protodeborylation. The addition of water to the anhydrous reaction system was considered to present disadvantages as compared to $K_3PO_4 \cdot nH_2O$. As it is well known, hygroscopic bases in the presence of water tend to aggregate and solidify to cause adhesion to the walls of the vessel. This hinders the progress of the reaction and makes lot-to-lot reproducibility more difficult. Based on these considerations, $K_3PO_4 \cdot nH_2O$ was chosen as the most suitable base for the process.

As the coupling reaction utilizes a two-phase system (solid–liquid) and $K_3PO_4 \cdot nH_2O$ has poor solubility in solvents such as toluene, the effect of the particle size of several brands of $K_3PO_4 \cdot nH_2O$ was investigated. We found that the high activity was obtained by $K_3PO_4 \cdot nH_2O$ of around 240 μm (50% cumulate particle diameter: 237 μm). Larger-sized K_3PO_4 (e.g. 50% cumulate particle diameter: 410 μm) had less contact area (Fig. 3).

2.2.3. Solvent

Several kinds of solvents have been used for the Suzuki–Miyaura reaction including alcohols (e.g. EtOH), ethers (e.g. DME), polar solvents (e.g. DMF), less polar solvents (e.g. toluene), and combinations of them with aqueous media. Although it has been reported that mixed solvent systems give good yields using boronates, the coupling reaction did not reach completion under these conditions. This was attributed to the decomposition of boronic ester caused by the aqueous base as well as an increase in the reductive debromination product (***R***)-**1c** without change in amount of **6b**. Experiments on the generation of (***R***)-**1c** revealed that it was generated in the presence of ethanol and that the water content of the reaction mixture had almost no effect. As aryl bromide (***R***)-**1b** is supplied as a solution in toluene, direct use of this solution as a starting material for the coupling reaction was convenient. Among the various solvents, toluene gave the best results.

2.2.4. Molar ratio of reagents

As shown in Table 3, although the minimum amount of $PdCl_2(PPh_3)_2$ required for consumption of (***R***)-**1b**

was 0.4 mol%, the optimum amount to ensure stable progress in large scale manufacturing is 1 mol%.

The amount of boronate **6b** was fixed at 1.5 equivalents based on a similar consideration. In fact, when 1.1 equivalents of **6b** were used, the coupling reaction did not reach completion ((***R***)-**5** yield: 82%).

Table 3
Effect of various amounts of $PdCl_2(PPh_3)_2$ on the coupling reaction of (***R***)-**1b** and **6b** [a]

Entry	Calalyst (mol%)	**6b** (equivalent)	Time (h)	Conversion [b] (%)
1	2	1.5	1	100
2	1	1.5	1.5	100
3	0.4	1.5	3	100
4	0.25	1.5	6	90
5	1	1.3	2	99
6	1	1.1	2	92

[a] $K_3PO_4 \cdot nH_2O$ was used as a base and toluene as a solvent.
[b] The term 'Conversion' means the ratio ((***R***)-**5**/((***R***)-**5**–(***R***)-**1b**)) calculated from HPLC relative area % of each compound.

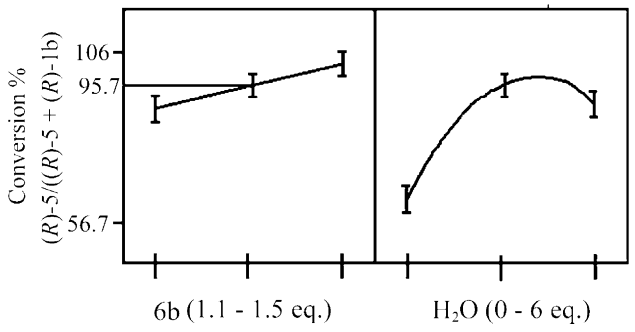


Fig. 4. Prediction plot of the conversion to (***R***)-**5** vs. equivalents of **6b** (left) and H_2O (right) for the optimization experiment by the central composite design.

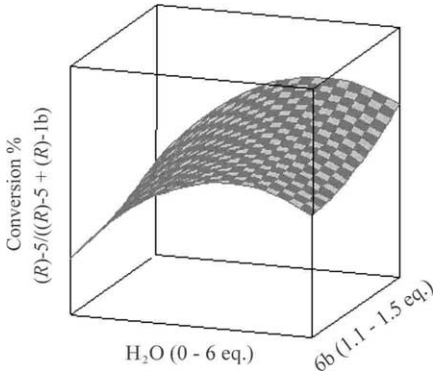


Fig. 5. The 3D contor plot for the central composite design. The *X*, *Y* and *Z*-variables are the equivalent of H_2O, equivalent of **6b** and the statistical conversion to (***R***)-**5**, respectively.

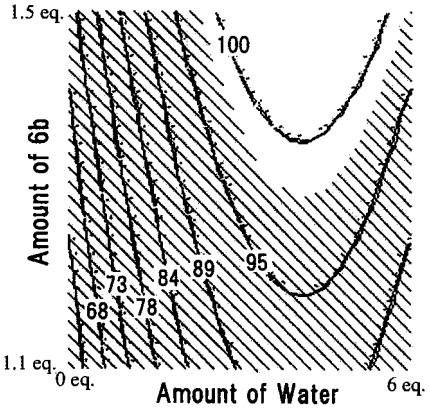


Fig. 6. Contor plot for the central composite design. The *X*- and *Y*-axes correspond to the equivalent of H_2O and the equivalent of **6b**. The statistical conversion values are shown in the plot.

Table 4
Comparison between the water contents of fresh or old $K_3PO_4 \cdot nH_2O$ bottles

State of $K_3PO_4 \cdot nH_2O$	Moisture %	Actual *n* [a]
Newly opened bottle	11.3	1.50
'Old' bottle	20.6	2.23

[a] The term 'Actual *n*' means the molar ratio (H_2O/K_3PO_4) calculated from moisture content.

2.3. Optimization of conditions for large-scale synthesis

We next proceeded to determine the optimum water content to increase yield and insure reproducibility.

2.3.1. Optimization by DOE

The design of experiment (DOE) approach was utilized to further optimize the conditions for the Suzuki–Miyaura reaction between (***R***)-**1b** and **6b**.

Using statistic analysis, we analyzed the amount of boronate **6b** and H_2O to bromide (***R***)-**1b**. As shown in Fig. 4, the yield of (***R***)-**5** varied linearly against the equivalent of boronate, indicating that more than 1.3 equivalents of **6b** was required to obtain biphenyl (***R***)-**5** with a yield of more than 96%. In contrast, the yield of (***R***)-**5** increased with water content and reached a peak at 3.7 equivalents of water, and then decreased.

To view this more clearly, we integrated the two graphs into 3D contor-line graphs in Figs. 5 and 6.

Thus, for 1.5 equivalents of boronate **6b**, the amount of water had to be in the range of 2.3–5.8 equivalents to obtain (***R***)-**5** with a yield of more than 98%. Although $K_3PO_4 \cdot nH_2O$ is usually available with 1.5 waters, this base is hygroscopic. The actual moisture in newly opened and 'old' bottles of $K_3PO_4 \cdot nH_2O$ is shown in Table 4.

The water content '*n*' in $K_3PO_4 \cdot nH_2O$ was in the range of 1.50–2.23. The amount of $K_3PO_4 \cdot nH_2O$ used

for our coupling reaction is 1.5 equivalents against bromide (***R***)-**1b**. When a new bottle of the reagent was used, water content was 2.3 equivalents, and if old one was used, the moisture was 3.3 equivalents Thus, appropriate moisture for 1.5 equivalents of **6b** was kept by using $K_3PO_4 \cdot nH_2O$.

2.3.2. Optimization of temperature and solvent volume

The temperature and volume of solvent required for the coupling reaction were then investigated. The coupling reaction proceeded smoothly at about 80–110 °C (refluxing in toluene) in almost equal yields. Thus, refluxing was chosen, because the temperature control was easy in a pilot plant.

With regards to the amount of solvent, the reaction was found to complete in toluene 5–15 times in volume of the weight of (***R***)-**1b** (Table 5).

2.4. Safety evaluation

Evaluation of the hazards of a reaction is indispensable for safe production in a pilot plant. The analysis of heat value of reactions as well as hazard evaluation by differential scanning calorimeter (DSC) and ARC analysis of reagents and reaction mixtures are all important factors. In particular, we needed to clarify the balance between reaction heat and cooling capacity, because the reaction started by mixing all the reagents in a reactor. Thermoanalytic data from reaction calorimerer (RC-1) are shown in Table 6.

The results obtained indicated that the total heat generated could be dissipated through the heat for vaporization of the solvent and cooling capacity of the reactor over 33 min. On the other hand, if the reaction was completed within a few minutes, there was significant danger. So, the amount of catalyst controls the reaction rate and is the most significant factor for the safe scaling-up.

Table 5
Conversions of the reaction with various volumes of solvent

Entry	Solvent volume [a]	Conversion [b] (%)
1	5	100
2	10	100
3	15	100

[a] The term 'Solvent volume' means the calculated volume/weight ratio (toluene/(***R***)-**1b**, unit: ml g^{-1}).

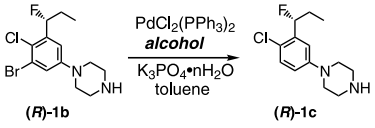
[b] The term 'Conversion' means the ratio ((***R***)-**5**/((***R***)-**5**–(***R***)-**1b**)) calculated from HPLC relative area % of each compounds.

Table 6
Heat value generated by the reaction

Reaction time (min)	0–30	30–90
Heat of reaction (kJ mol^{-1})	476	41

Heat values were measured and analyzed by RC-1 ((***R***)-**1b** 30 g scale).

Table 7
Reaction in the presence of alcohols (1.5 equivalents)



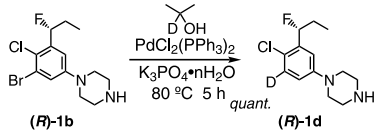
Entry	Alcohol	Conversion [a] (%)
1	1,3-Propanediol	61
2	Pinacol	4.5

[a] The term 'Conversion' means the ratio ((***R***)-**1c**/((***R***)-**1b**–(***R***)-**1c**)) calculated from HPLC relative area % of each compounds.

2.5. Mechanistic study

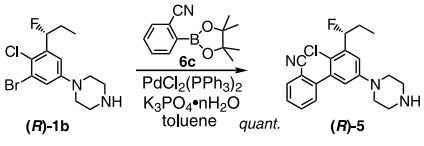
The method developed so far was efficient to obtain the desired coupling product (***R***)-**5** using boronic ester **6b** in more than 90% yield. Our next step was to identify and reduce the impurities to bring up the yield of the reaction. We identified the main impurity as the reductive debromination compound (***R***)-**1c**. However, homo-coupling compound of (***R***)-**1b** and CN-hydrolyzation compound which are common impurities in the cross-coupling were not detected. As (***R***)-**1c** increased gradually with the progress of reaction, a reduction route appeared to be associated with the reaction. Treatment of (***R***)-**1b** under the same reaction conditions and in the absence of **6b** gave (***R***)-**1c** in very low amounts. When (***R***)-**1b** was treated with 1.5 equivalents of 1,3-propanediol or pinacol instead of **6b**, the conversion of (***R***)-**1c** was 61 or 4.5%, respectively (Table 7).

These results suggest that reduction has mainly proceeded by migration of α-H in 1,3-propanediol to palladium atom of aryl-palladium complex. This was supported by the fact that the use of Me_2CDOH as a solvent in the absence of **6b** gave a deuterized compound (***R***)-**1d** quantitatively (Eq. (4)).



(4)

It is unclear yet whether this competitive reduction is caused by free 1,3-propanediol or by boronate concertedly. The coupling of (***R***)-**1b** with pinacol boronate **6c** that has no α-H afforded the desired product quantitatively (Eq. (5)).



(5)

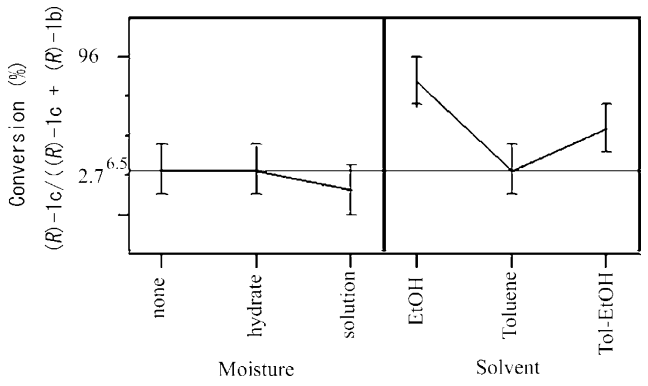


Fig. 7. Prediction plot of the conversion to (***R***)-**1c** vs. the equivalent of water (left) and solvents (right) for the optimization experiment by full factorial design.

From the viewpoint of selectivity, toluene is a favorable solvent because the reactions in the alcohols bearing α-H (e.g. EtOH) induced reductive debromination (Fig. 7).

The proposed mechanism for the cross-coupling reaction is shown in Scheme 4. A plausible pathway for the formation of (***R***)-**1c** is also presented, wherein an alcohol plays a role as a hydride donor in the production of (***R***)-**1c**.

As indicated above, reductive dehalogenation is a major side reaction of (***R***)-**1b**. Investigation into this phenomenon is indispensable to improve the impurity profile and is being studied at present.

2.6. Application

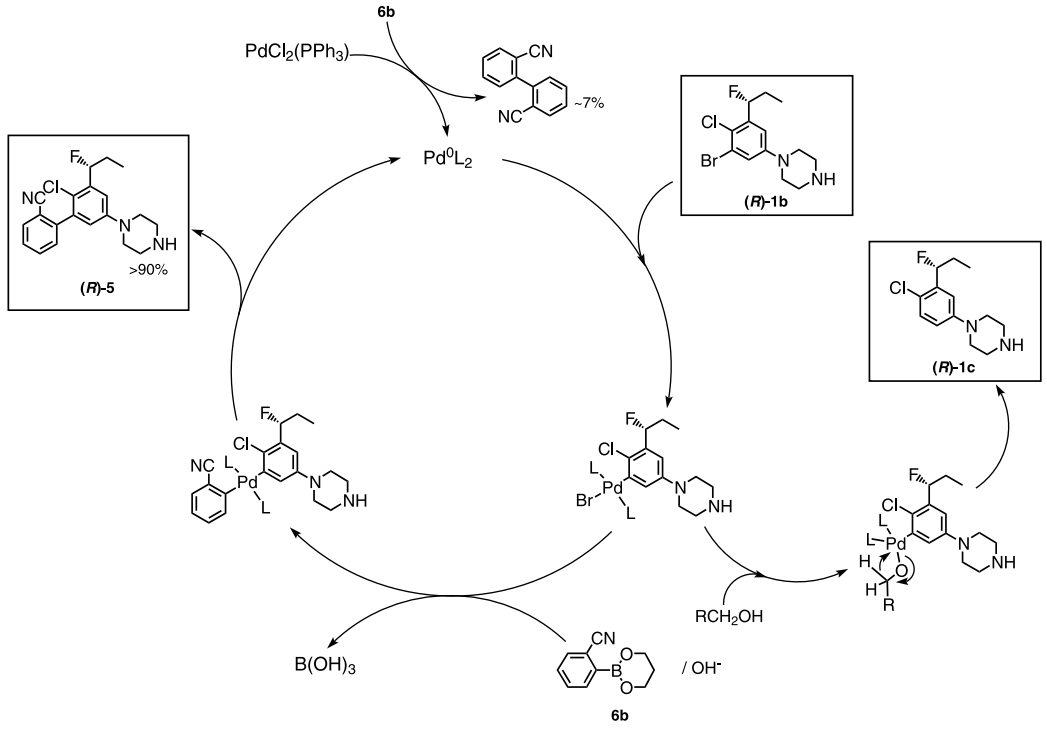
Lastly, we explored the applicability of the cross-coupling reaction under the conditions selected. As the introduction of the cyanophenyl moiety is useful for synthesis of various API, coupling of boronate **6b** with some other bromides was studied. Bulky and electron-rich bromides also reacted to give the corresponding biphenyls in excellent yields.

On the contrary, the reaction of the corresponding triflate resulted in low yield (24%) because of hydrolysis of the substrate. As triflates are distinctly more active materials than bromides, the coupling with **6b** smoothly proceeded under anhydrous conditions (yield: 86%, Table 8).

In short, the cyanophenyl moiety was efficiently prepared using both bromides and triflates.

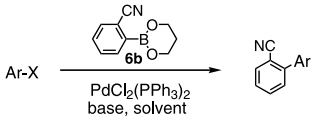
3. Conclusion

A highly reliable and efficient synthetic method for E2040 drug substance was established by the Suzuki–Miyaura coupling reaction using unstable (*o*-cyanophenyl)boronic ester. It was found that the biaryl moiety bearing an electron-withdrawing group at an *ortho*-position can be prepared in an efficient fashion and the reaction conditions employed were optimized utilizing DOE approach. Safety evaluation was conducted and the reaction in a pilot plant was ensured. A



Scheme 4.

Table 8
Coupling of **6b** with various substrate



Entry	Ar	X	Base	Solvent	Yield [a]
1	2-$(CH_3O)C_6H_4$	Br	$K_3PO_4{\cdot}nH_2O$	Toluene	99
2	2,4-$(CH_3O)_2C_6H_3$	Br	$K_3PO_4{\cdot}nH_2O$	Toluene	76 (98)
3	2,6-$(CH_3)_2C_6H_3$	Br	$K_3PO_4{\cdot}nH_2O$	Toluene	92
4	4-$(CH_3)C_6H_4$	Cl	$K_3PO_4{\cdot}nH_2O$	Toluene	(2)
5	4-$(CH_3)C_6H_4$	Br	$K_3PO_4{\cdot}nH_2O$	Toluene	(97)
6	4-$(CH_3)C_6H_4$	I	$K_3PO_4{\cdot}nH_2O$	Toluene	(99)
7	4-$(CH_3)C_6H_4$	OTf	$K_3PO_4{\cdot}nH_2O$	Toluene	(24)
8	4-$(CH_3)C_6H_4$	OTf	K_3PO_4	DMF	(86)

[a] Isolated yields. HPLC yields are in parentheses.

mechanism for reductive debromination is proposed; this side reaction seems to be suppressed by use of boronic ester having no α-H. Applications to conversion of electron-rich and/or sterically hindered aryl bromides were also performed in good yields. Further capacity of our reaction conditions for the synthesis of other compounds is currently under investigation.

4. Experimental

4.1. General method

M.p. were determined with a Yamato MP-21 melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL α-400 spectrometer. Chemical shifts for ^{1}H-NMR are reported in ppm downfield (δ) relative to Me_4Si as an internal standard in $CDCl_3$ or Me_2SO-d_6 and are reported in ppm. Residual heavy metal levels were measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES) on a Perkin–Elmer Optima 3300DV. HPLC was performed on a JASCO LCSS-900 or TOSOH SC8020 system equipped with a YMC Pro C-18 column (unless otherwise specified) and an UV detector. Elemental analyses were obtained from Toray Research Center, Inc. Potassium phosphate hydrate was purchased from Kishida Chemical Co., Ltd. (unless otherwise specified). Other reagents are commercially available and were used without further purification.

4.1.1. Preparation of 1-{3-bromo-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine ((*R*)-**1b**)

This compound was prepared as a pale yellow oil by previously reported method [1].

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.04 (t, $J = 7.2$ Hz, 3H), 1.70 (bs, 1H), 1.72–2.02 (m, 2H), 3.00–3.02 (m, 4H), 3.13–1.16 (m, 4H), 5.70 (ddd, $J = 3.6$, 8.5 and 47.6 Hz, 1H), 6.97 (d, $J = 2.8$ Hz, 1H), 7.09 (d, $J = 2.8$ Hz, 1H). Anal. Calc. for $C_{13}H_{17}BrClFN_2$: C, 46.52; H, 5.11; N, 8.35. Found: C, 46.48; H, 5.13; N, 8.13%.

4.1.2. Optimization by DOE

The experimental design was generated using JMP® Version 4 software (SAS Institute).

A central composite design was implemented to optimize the amount of **6b** and H_2O against (*R*)-**1b** for preparation of (*R*)-**5**. A set of 10 individual experiments contained eight reactions with combinations of different amounts of **6b** and H_2O as well as two center points (1.3 equivalents of **6b**, three equivalents of H_2O). The stoichiometric ratios of **6b** and H_2O were 1.3–1.5 and 0–6 equivalents, respectively. After the reaction mixture was heated at 100 °C under stirring for 30 min and 2 h, aliquots of samples were taken for HPLC assay. The yields of the reactions were calculated based on HPLC assay with 2,7-dimethoxynaphthalene as an internal standard. The data were analyzed by JMP® Version 4 software.

4.1.3. ARC measurements

A Columbia Scientific Industries ARC machine with a stainless steel bomb was used as follows: sample mass, ca. 2 g; thermal inertia factor (PHI factor), ca. 4; start temperature, 35 °C; end temperature, 400 °C; slope sensitivity, 0.02 °C min^{-1}; heat step temperature, 5 °C; calibration temperature step, 0.2 °C; wait time, 10 min.

4.1.4. Preparation of 1-{3-(2-cyanophenyl)-4-chloro-5-[1-(R)-fluoropropyl]}phenyl piperazine ((*R*)-**5**) and its (+)-di-p-toluoyl-D-tartaric acid salt ((*R*)-**5**·**1**/**2DTTA**)

To a solution of 35.3 g (assay: 92.5%, 97.3 mmol) of 1-{3-bromo-4-chloro-5-[1-(*R*)-fluoropropyl]}phenyl-

piperazine ((***R***)-**1b**), 683 mg (0.97 mmol) of dichlorobis(triphenylphosphine)palladium and 27.3 g (146 mmol) of 2-(1,3,2-dioxaborinan-2-yl)benzonitrile in 177 ml of $C_6H_5CH_3$ at room temperature (r.t.) was added 36.2 g (146 mmol) of tripotassium phosphate hydrate. The reaction mixture under nitrogen atmosphere was then heated while refluxing for 1.5 h to make most of (***R***)-**1b** consumed. The mixture was allowed to cool to r.t. and to this was added 180 ml of water to conduct partition and the organic layer was washed with 180 ml of water (residual Pd after concentration was 2544 ppm). To this organic layer was added 64 g of CR-20® and was stirred for 17 h. CR-20® was removed by filtration and the filtrate was concentrated to give 43.4 g of crude (***R***)-**5** as a yellow viscous oil (assay: 70.1%, yield: 87%).

To a stirred solution of 14.5 g (37.6 mmol) of (+)-di-*p*-toluoyl-D-tartaric acid in 224 ml of C_3H_6O containing 67 ml of water was added a solution of 32.0 g (assay: 70.1%, 62.6 mmol) of crude (***R***)-**5** in 224 ml of C_3H_6O containing 67 ml of water over 30 min at r.t. The mixture was then heated at 60 °C and maintained at this temperature while stirring for 5 h. The mixture was allowed to cool to r.t. and stirred for 16 h. The precipitates were collected by filtration and washed with aq. C_3H_6O, then dried to a constant weight in oven (60 °C) to give 28.6 g of (***R***)-**5·1/2DTTA** (yield: 81% from crude (***R***)-**5**, residual Pd: 22 ppm).

*4.1.4.1. (**R**)-**5**.* ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.08 (t, $J = 7.2$ Hz, 3H), 1.82–2.10 (m, 2H), 3.01–3.04 (m, 4H), 3.18–3.20 (m, 4H), 5.78 (ddd, $J = 3.2$, 7.6 and 47.2 Hz, 1H), 6.79 (d, $J = 2.8$ Hz, 1H), 7.11 (d, $J = 2.8$ Hz, 1H), 7.43 (d, $J = 7.6$ Hz, 1H), 7.48 (t, $J = 7.6$ Hz, 1H), 7.64 (t, $J = 7.6$ Hz, 1H), 7.75 (d, $J = 7.6$ Hz, 1H). Anal. Calc. for $C_{20}H_{21}ClFN_3$: C, 67.13; H, 5.91; N, 11.74. Found: C, 67.31; H, 6.00; N, 11.43%.

*4.1.4.2. (**R**)-**5·1/2DTTA**.* ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.07 (t, $J = 7.6$ Hz, 3H), 1.80–2.10 (m, 2H), 2.21 (s, 3H), 3.00–3.20 (m, 8H), 5.50 (s, 1H), 5.77 (ddd, $J =$ 3.2, 8.4 and 47.2 Hz, 1H), 6.64 (d, $J = 2.8$ Hz, 1H), 6.89 (d, $J = 2.8$ Hz, 1H), 6.98 (d, $J = 8.4$ Hz, 2H), 7.32–7.44 (m, 4H), 7.79 (d, $J = 8.4$ Hz, 2H), m.p. 197–199 °C (dec.). Anal. Calc. for $C_{30}H_{30}ClFN_3O_4$: C, 65.39; H, 5.49; N, 7.63. Found: C, 65.19; H, 5.54; N, 7.61%.

4.1.5. Preparation of arylboronic esters

*4.1.5.1. 2-(1,3,2-Dioxaborinan-2-yl)benzonitrile (**6b**).* This compound was prepared in 49% yield from 2-bromobenzonitrile (according to patent) [1].

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.10 (p, $J = 5.6$ Hz, 2H), 4.23 (t, $J = 5.6$ Hz, 4H), 7.48 (t, $J = 7.6$ Hz, 1H), 7.54 (t, $J = 7.6$ Hz, 1H), 7.67 (d, $J = 7.6$ Hz, 1H), 7.87 (d, $J = 7.6$ Hz, 1H), m.p. 47–50 °C. Anal. Calc. for $C_{10}H_{10}BNO_2$: C, 64.23; H, 5.39; N, 7.49. Found: C, 64.03; H, 5.43; N, 7.47%.

*4.1.5.2. 2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)benzonitrile (**6c**).* This compound was prepared in a quantitative yield from 2-cyanophenylboronic acid in the manner as above using pinacol instead of 1,3-propanediol.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 12H), 7.53 (t, $J = 7.2$ Hz, 1H), 7.57 (t, $J = 7.2$ Hz, 1H), 7.70 (d, $J = 7.2$ Hz, 1H), 7.88 (d, $J = 7.2$ Hz, 1H), m.p. 74–77 °C. Anal. Calc. for $C_{13}H_{16}BNO_2$: C, 68.16; H, 7.04; N, 6.11. Found: C, 68.03; H, 6.96; N, 6.17%.

*4.1.6. Comparison between **6b** and **6c***

Experiments using **6b** or **6c** were carried out three times with an automated equipment (L-COS 24 [12]).

At the beginning of the experiment, each sample vial was loaded with 95% aq. MeOH (1.5 ml) to quench the samples ahead of HPLC analysis. Each reaction vial is charged with potassium phosphate hydrate (333 mg, 1.34 mmol) and **6b** (250 mg, 1.34 mmol) or **6c** (306 mg, 1.34 mmol) and to this was added a $C_6H_5CH_3$ solution (5 ml) containing (***R***)-**1b** (300 mg, 18 mmol), dichlorobis(triphenylphosphine)palladium (II) (6.0 mg, 0.17 mmol) and 2,7-dimethoxynaphthalene (50 mg, 5.3 mmol). After heating at 100 °C for 2 h, aliquots of each agitated reaction mixture was injected into the sample vial and analyzed by HPLC. The data were analyzed by JMP® Version 4 software.

*4.1.7. Preparation of 1-{4-chloro-3-[1-(R)-fluoropropyl]}phenylpiperazine ((**R**)-**1c**)*

A stirred mixture of 1.04 g (3.1 mmol) of 1-{3-bromo-4-chloro-5-[1-(*R*)-fluoropropyl]}phenylpiperazine ((***R***)-**1b**), 86.9 mg (0.12 mmol) of dichlorobis(triphenylphosphine)palladium at r.t. and 1.15 g (4.6 mmol) of tripotassium phosphate hydrate (2.2 hydrate) in 5 ml of 2-butanol was heated at 100 °C for 2.5 h to make most of (***R***)-**1b** consumed. The mixture was allowed to cool to r.t. Water (5 ml) was added to the resulting mixture to conduct partition. The organic layer was washed with brine and to this was added 2 ml of ethylendiamine while stirring. The mixture was stirred for 2 h. Black precipitates were removed by filtration and the filtrate was concentrated to give 0.68 g of crude (***R***)-**1c**.

To a stirred solution of 690 mg (1.8 mmol) of (+)-di-*p*-toluoyl-D-tartaric acid in 4 ml of C_3H_6O containing 1.2 ml of water at r.t. was added a solution of crude (***R***)-**1c** in 4 ml of C_3H_6O containing 1.2 ml of water. The mixture was stirred for 1.5 h, and then all the precipitates were collected by filtration and washed with aq. C_3H_6O, then dried to a constant weight in oven (60 °C) (1.03 g, yield: 74.1% as white crystals).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.05 (t, $J = 7.2$ Hz, 3H), 1.76–2.04 (m, 2H), 2.34 (s, 3H), 3.14–3.34 (m, 8H), 5.36 (s, 1H), 5.71 (ddd, $J = 4.0$, 8.0 and 47.2 Hz, 1H), 6.70 (dd, $J = 3.2$ and 8.8 Hz, 1H), 6.96 (d, $J = 3.2$ Hz, 1H), 7.08 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.8$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), m.p. 175–177 °C (dec.).

4.1.8. Measurement of heats of reaction

A Mettler's RC1 reaction calorimeter outfitted with an SV-01 batch reactor (0.8 l glassware) was used. (***R***)-**1b** (30 g), **6b** (25 g), $PdCl_2(PPh_3)_2$ (1.23 g), $K_3PO_4{\cdot}nH_2O$ (32 g) and $C_6H_5CH_3$ (450 ml) were charged in the reactor, and the mixture was heated at 100 °C under nitrogen atmosphere. The measurement of the heat was continued until heat generation and consumption of (***R***)-**1b** came to a period. Calibrations to determine the heat capacity and the heat transfer coefficient were performed before and after the reaction. The heat of reaction was measured to be 476 (0–30 min) and 41 kJ mol^{-1} (30–90 min).

4.1.9. General procedure for preparation of 2′-substituted aryl 2-benzonitrile

A stirred mixture of 560 mg (3.0 mmol) of 2-bromoanisole, 21 mg (0.03 mmol) of dichlorobis(triphenylphosphine)palladium, 0.84 g (4.5 mmol) of **6b** and 1.03 g (1.5 mmol) of tripotassium phosphate hydrate (2.2 hydarate) in 5 ml of $C_6H_5CH_3$ was heated under reflux for 1 h to confirm consumption of 2-bromoanisole. The mixture was allowed to cool to r.t. To this was added water to conduct partition. The organic layer was washed with water and concentrated. The oil obtained was purified by a silica gel chromatography to give 620 mg of 2′-methoxy-biphenyl-2-carbonitrile as an oil (yield: 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H), 7.03 (d, $J = 8.8$ Hz, 1H), 7.06 (t, $J = 7.6$ Hz, 1H), 7.26 (d, $J = 7.2$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 2H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.62 (t, $J = 7.6$ Hz, 1H), 7.72 (d, $J = 7.2$ Hz, 1H).

4.1.9.1. 2′,5′-Dimethoxybiphenyl-2-carbonitrile (white crystal, yield: 76%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 3.86 (s, 3H), 6.57, (s, 1H), 6.59 (d, $J = 8$ Hz, 1H), 7.18 (d, $J = 8$ Hz, 1H), 7.38 (t, $J = 8$ Hz, 1H), 7.45 (d, $J = 8$ Hz, 2H), 7.59 (t, $J = 8$ Hz, 1H), 7.70 (d, $J = 8$ Hz, 1H), m.p. 84–86 °C. Anal. Calc. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.02; H, 5.50; N, 5.96%.

4.1.9.2. 2′,6′-Dimethylbiphenyl-2-carbonitrile (white crystal, yield: 92%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 6H), 7.14 (d, $J = 8$ Hz, 2H), 7.32 (t, $J = 8$ Hz, 1H), 7.29 (d, $J = 8$ Hz, 1H), 7.46 (t, $J = 8$ Hz, 1H), 7.66 (t, $J = 8$ Hz, 1H), 7.77 (d, $J = 8$ Hz, 1H), m.p. 94–96 °C. Anal. Calc. for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.32; H, 6.39; N, 6.76%.

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