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Re-evaluation of *P*-Chiral, *N*-Phosphoryl Sulfonamide Brønsted Acids in the Asymmetric Synthesis of 1,2,3,4-Tetrahydroquinoline-2-carboxylate Esters via Biomimetic Transfer Hydrogenation

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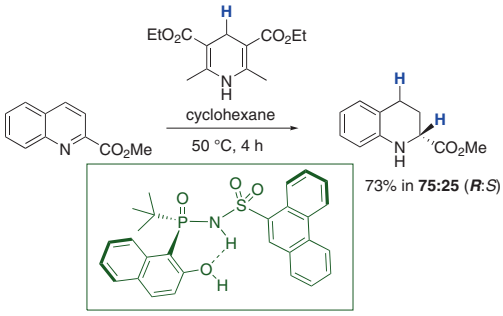

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Abstract Enantioenriched heterocyclic and rigidified bioisosteres of amino acids are valuable building blocks in drug discovery, particularly in the design of peptidomimetic drugs. The rigidified bioisostere of phenylalanine, 1,2,3,4-tetrahydroquinoline-2-carboxylic acid, is found in several biologically active compounds. However, only a small number of successful methodologies have been reported for its asymmetric synthesis. To develop an environmentally benign and metal-free organocatalytic process for the preparation of this compound, a number of novel *P*-chiral, *N*-phosphoryl sulfonamide Brønsted acids were synthesized and evaluated in a biomimetic transfer hydrogenation reaction of quinoline-2-carboxylates to give the (*R*)-1,2,3,4-tetrahydroquinoline-2-carboxylates.

Key words Brønsted acid catalysis, transfer hydrogenation, asymmetric synthesis

Chiral molecules that can serve as bioisosteres of amino acids constitute valuable building blocks for medicinal chemistry, particularly in the synthesis of biologically active peptidomimetics. These bioisosteres often play a significant role in optimizing the biopharmaceutical properties of human therapeutics, improving their cell-based potency, metabolic stability, solubility in biological fluids and oral bioavailability.[1] Examples of such enormously valuable building blocks are those characterizing the structures of the clinically validated drugs shown in Figure 1.

Amino acid bioisosteres also serve as precursors in the synthesis of other chiral molecules that are equally valuable in medicinal chemistry and organic synthesis/catalysis (Figure 2). Examples include intermediates **6** and **7**, which have been used in the preparation the chiral *N*-heterocyclic carbene ligand (NHC) of the Ru-based catalyst **9**,[2] and the multikilogram production of the Bcl-2/Bcl-x_L dual antagonist **10**,[3] respectively (Figure 2). For both of these examples, the rigidified phenylalanine bioisostere **8** was used as the starting material, which was initially accessed from the hydrogenation of inexpensive and commercially available quinoline-2-carboxylic acid.[2,3]

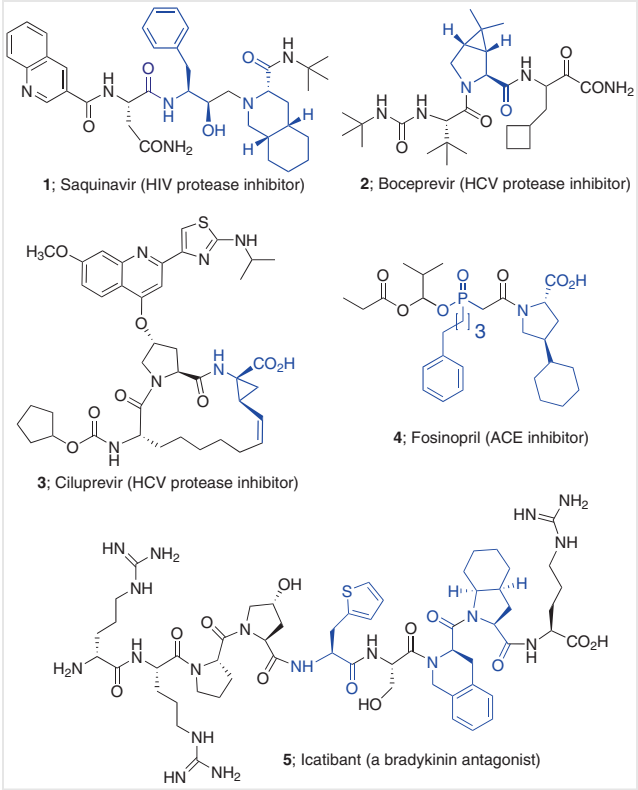

Figure 1 Examples of amino acid bioisosteres (highlighted in blue) in human therapeutics

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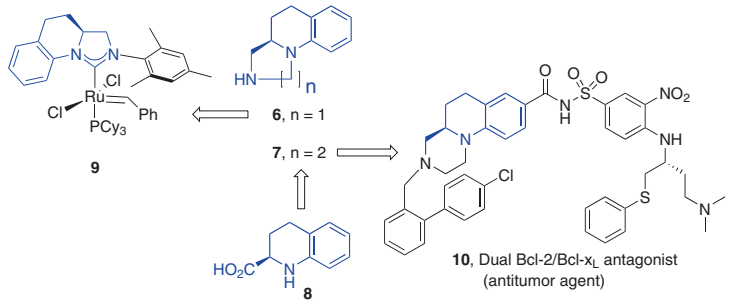
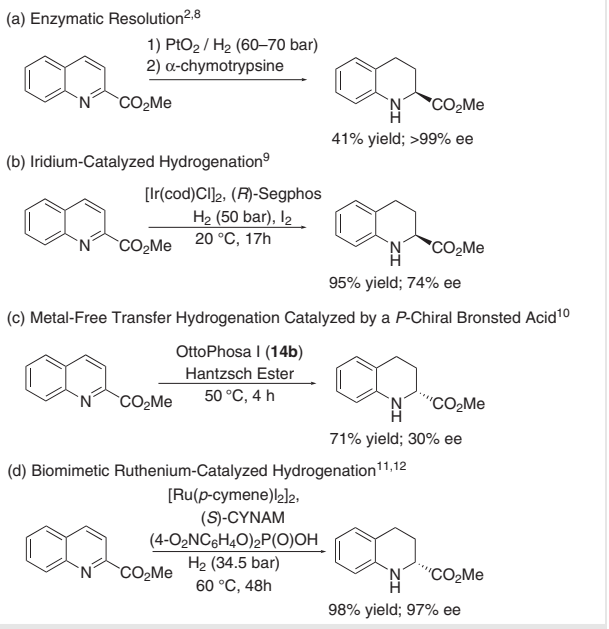


Figure 2 An example of a chiral ligand (**9**) and a human therapeutic (**10**), synthesized from chiral tetrahydroquinoline-2-carboxylic acid (**8**)

Tetrahydroquinoline scaffolds are a common structural motif of biologically active natural products and human therapeutics.[4] A number of efficient methodologies have already been reported on the asymmetric synthesis of such compounds that include metal-catalyzed asymmetric hydrogenation,[5] as well as biomimetic transfer hydrogenation catalyzed by Brønsted acids,[6] of their precursor quinolines. However, a very limited number of reports describe the asymmetric hydrogenation of quinolines having a C-2 electron-withdrawing substituent, such as a ketone, carboxylic acid, amide or ester moiety (Scheme 1).



Scheme 1 Asymmetric hydrogenation of quinoline-2-carboxylate methyl ester

In the course of our medicinal chemistry investigations, enantioenriched tetrahydroquinoline-2-carboxylic acid (Figure 2; **8**) was required for the preparation of peptidomimetic inhibitors targeting the zinc metalloprotease STE24 (ZMPSTE24).[7] Earlier reports on the synthesis of **8** (as its methyl ester) directly from the quinoline-2-carboxylate methyl ester include classical hydrogenation followed by enzymatic separation of the enantiomers (Scheme 1a),[8] iridium-catalyzed asymmetric hydrogenation of quinoline-2-carboxylate ester (Scheme 1b),[9] and biomimetic, metal-free transfer hydrogenation catalyzed by a *P*-chiral, *N*-phosphoryl sulfonamide Brønsted acid (Scheme 1c).[10] Most recently, a very efficient Ru-catalyzed asymmetric reduction that utilizes a regenerable bioisostere of NADH/NADPH [(S)-CYNAM][11] and a Brønsted acid (Scheme 1d) was also reported.[12]

Phosphorus-based Brønsted acids are highly valuable organocatalysts,[6] with the BINOL-based derivatives catalyzing numerous transformations. These organocatalysts were first reported by Akiyama[13] and Terada,[14] and have been reported to catalyze a plethora of asymmetric reactions, including Mannich-type[13a,14,15] and Diels–Alder reactions,[16] the enantioselective hydrophosphonylation of imines,[17] reductive aminations,[18] imine transfer hydrogenations,[19] Friedel–Crafts alkylations,[20] intramolecular Michael additions,[21] the *N*,*O*-acetalization of aldehydes[22] and the transfer hydrogenation of various heterocyclic compounds.[6,23] These Brønsted acids were also reported to catalyze metal-free asymmetric 6π-electrocyclization reactions, leading to enantiomerically enriched 1,4-dihydropyridazines.[24] BINOL-based dimeric and sterically highly confined imidodiphosphorimidate analogs were designed by List,[25] and shown to catalyze the formation of highly enantioenriched five- and six-membered ring ethers from the intramolecular nucleophilic attachment of an alcohol onto a double bond.[25a] Additionally, these molecules can also catalyze enantioselective C–C bond formation in Mukaiyama aldol-type reactions at remarkably low concentration of the catalyst.[25b]

P-Chiral, *N*-phosphoryl sulfonamide Brønsted acids, such as **12**, were originally reported by Han, Senanayake and co-workers,[26] and were used in the transfer hydrogenation of quinolines to tetrahydroquinolines with modest enantioselectivity (e.g., Table 1, entry 1). We speculated that the introduction of an intramolecular hydrogen bond/ion pair (Figure 3; e.g., **13**),[10] could modulate the catalytic activity of these organocatalysts, stabilizing the conformation of the catalytic cavity, and potentially acting as a 'hydride

shuttle', which could lead to significant acceleration of the reaction rate and increase in enantioselectivity.[10]

During our initial evaluation of organocatalyst **13**, we observed a dramatic acceleration of the reaction rate and substantial improvement in enantioselectivity, when compared to **12** (Table 1, entry 1 vs. 2).[10] After some screening of the aromatic substituent attached to the phosphorus atom,[10] the optimized analog OttoPhosa I (**14b**) was identified and found to further increase enantioselectivity to 80% ee (entry 3). We were also pleased to find that analog **14b** could catalyze the asymmetric transfer hydrogenation of the methyl quinoline-2-carboxylate **11** (R^2=CO_2Me, R^6=H) to the corresponding methyl (*R*)-1,2,3,4-tetrahydroquinoline-2-carboxylate (**8**), albeit with much lower enantioselectivity and only at higher temperature (entry 4). The basicity of the quinoline nitrogen plays a major role in the rate of this reaction and, consequently, it is not surprising that electron-withdrawing substituents at the C-2 carbon decelerate the reaction rate. In fact, our previous report is the first example of a Brønsted acid catalyzed transfer hydrogenation of quinoline-2-carboxylate (**11**; R^6=H).[10] However, after further evaluation of Brønsted acid **14b**, we observed significant decomposition of this molecule at high temperature. The decomposition of **14b** was followed by ^{31}P NMR (in $CDCl_3$) and it was found to begin within 5 hours at 40 °C and lead almost quantitatively to the racemic phosphonamidate **15** within 24 hours (Figure 3). The structure of this rearranged product (**15**) was confirmed by its single-crystal X-ray structure (Figure 4).

In the last decade alone, numerous [1,2]-phospha-Brook rearrangements have been employed in synthetic methodologies. Examples include the preparation of optically active phosphoric esters,[27] Brønsted base catalyzed [2,3]-Wittig rearrangements of 2-allyloxy-2-phosphonoacetates,[28] intramolecular cyclization of alkynyl α-ketoanilide,[29] asymmetric organocatalytic reductive coupling of benzylidene pyruvates and aldehydes,[30] the synthesis of 3-aryloxindoles,[31] preparation of 2,3-allenylamides,[32] Brønsted base catalyzed three-component coupling reactions of α-ketoesters, imines and diethyl phosphite,[33] intramolecular addition of benzyl anion to alkyne,[34] the generation of homoenolate equivalent compounds,[35] preparation of tetrasubstituted furans,[36] transformation of α,β-epoxyketones to allylic alcohols,[37] and the fluorinative ring expansion of 2-benzoylpyrrolidines.[38] Most recently, the use of this rearrangement has also been reported in the preparation of (difluoromethyl)cycloalkenes,[39] the Passerini–Smiles reaction of α-ketophosphonates,[40] and the asymmetric synthesis of enantioenriched axial chiral allenes.[41] All of the above mentioned reactions proceed under basic conditions, and examples of a Lewis acid catalyzed reaction are extremely rare.[42] To our knowledge, the Brønsted acid catalyzed [1,4]-phospha-Brook rearrangements observed in this study, for the conversion of organocatalyst **14b** into the phosphonamidate **15**, has not been previously reported. At high temperatures, it is likely that the electron-deficient phosphorus atom of **14b** can drive the nucleophilic attachment of the phenol to induce the rearrangement. It is also plausible that during the transfer hydrogenation of **11** to give **8**(Table 1) the accumulating 1,2,3,4-tetrahydroquinoline product (Figure 5; Path A; i.e., during the 2nd step of the catalytic cycle) is sufficiently basic to hydrogen-bond or deprotonate the weakly acidic phenol and accelerate an [1,4]-phospha-Brook rearrangement (Figure 5; Path B). The latter mechanism may explain why even at slightly higher temperatures (from 35 to 50 °C, corresponding to the temperatures at which **14b** is fairly stable and unstable, respectively, over a period of 4 hours) there is no significant deterioration of the enantioselectivity. Another possibility is that intramolecular rearrangement, involving a configurationally labile trigonal bipyramidal intermediate on the phosphorus atom, may be involved in the formation of **15**; such intermediates

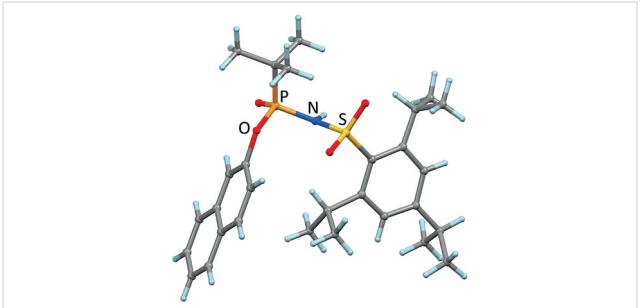


Figure 4 Single-crystal X-ray structure of racemic phosphonamidate **15**

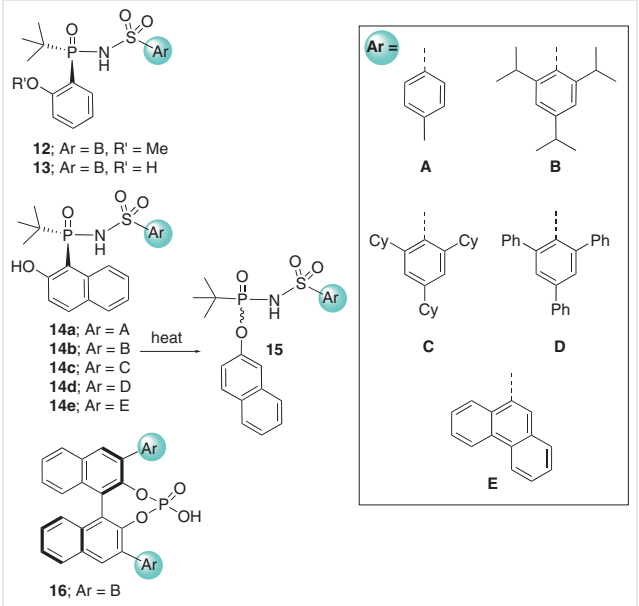


Figure 3 Brønsted acid catalysts explored in the transfer hydrogenation of quinoline-2-carboxylate methyl ester

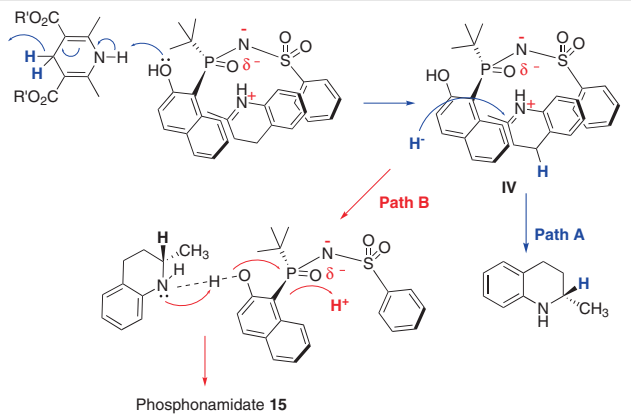


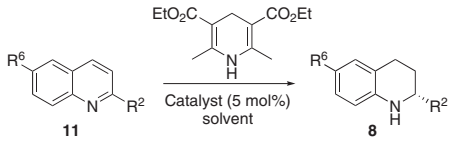
Figure 5 Plausible mechanism for the [1,4]-phospha-Brook rearrangement of organocatalyst **14b** to the phosphonamidate **15**

have been proposed in the racemization of *P*-chiral SPOs in the presence of $LiAlH_4$.[43]

In the hope of identifying a better organocatalyst within this structural class of Brønsted acids, which could catalyze the asymmetric hydrogenation of quinolines having a C-2 electron-withdrawing group at low temperatures and in higher enantioselectivity, we turned our attention to the role of the sulfonamide moiety. Several new derivatives were synthesized (Figure 3; analogs **14a**, **14c**,**d**,**e**) in order to evaluate the relative contributions to thermal stability and ability to induce enantioselectivity in the transfer hydrogenation specifically of quinoline-2-carboxylate methyl esters (**11**).

Initially, we carried out these reactions at 35 °C, which was found to be the highest temperature at which catalyst **14b** was chemically stable over a period of 48 hours. Interestingly, when the catalytic properties of Brønsted acid **14b** were compared with those of **14a** and **14c**, having a less sterically congested and a more sterically congested catalytic cavity, respectively, the reaction rates and yields were found to be virtually identical, and only a slightly higher enantiomeric excess of the product was observed with **14a** and **14c**, as compared to **14b** (Table 1; entries 5–7). Although these differences are very small, they suggested that steric hindrance may not play a very significant role in inducing enantioselectivity in this transformation. However, a more extended aromatic system on the sulfonamide moieties, such as analog **14d** and **14e**, lead to significantly different outcomes. Whereas Brønsted acid **14e** catalyzed the transfer hydrogenation of **11** to **8** with higher enantiomeric excess (entry 9), **14d** led to a completely racemic product (entry 8). These results seem to suggest that π-stacking interaction plays an important role in directing the binding of quinoline **11** within the catalytic cavity, allowing for the formation of a salt-bridge with the nitrogen or the oxygen anion, or even a bifurcated interaction with both. However, π-stacking interactions distal to the N^-/O^- may be detrimental in controlling the orientation of substrate binding. In spite of some decomposition of catalyst **14e** at higher temperatures (presumably due to the equivalent rearrangement product as **15**, these decomposition products did not appear to have any significant catalytic function), since increasing the temperature of the reaction to 50 °C led to 100% conversion (75% isolated yield) over a 4 h period with equivalent enantioselectivity (44–45% ee, entry 9 vs. 10). This result also suggests that catalyst loading lower than 5% may be sufficient to catalyze this reaction, albeit with a longer reaction time. We also confirmed that, in the absence of an organocatalysts, the transfer hydrogenation of **11** to **8** did not proceed at all, even at 50 °C temperature and over the same period (entry 10 vs. 11 and 14). To further validate the unique catalytic properties of compound **14e**, the same reaction was also run using the commercially available Brønsted acid **16** [(*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrogenphosphate;(*R*)-TRIP] at both 35 °C and 50 °C, and for an extended reaction period

Table 1 Asymmetric Transfer Hydrogenation of Quinolines[a]



Entry	Cat	R^2/R^6	Temp. (°C)	Time (h)	Solvent	Yield (%)[a]	ee (%)[b]
1	**12**	Me/Br	22	48	Tol	75	40
2	**13**	Me/Br	22	2	Tol	99	58
3	**14b**	Me/Br	22	2	Tol	99	80 (93)[c]
4	**14b**	CO_2Me/H	50	4	Cy	71	30
5	**14a**	CO_2Me/H	35	12	Tol	71	23
6	**14b**	CO_2Me/H	35	12	Tol	70	13
7	**14c**	CO_2Me/H	35	12	Tol	72	26
8	**14d**	CO_2Me/H	35	12	Tol	73	0
9	**14e**	CO_2Me/H	35	12	Tol	73	45
10	**14e**	CO_2Me/H	50	4	Tol	75	44
11	none	CO_2Me/H	50	48	Tol	0	–
12	**16**	CO_2Me/H	50	4	Tol	0	–
13	**14e**	CO_2Me/H	50	4	Cy	73	49
14	none	CO_2Me/H	50	4	Cy	0	–
15	**14e**	CO_2Me/F	50	4	Cy	83	48
16	**14e**	CO_2Me/Br	50	4	Cy	76	46 (66)[d]

[a] The absolute stereochemistry was assigned based on comparison of the chiral HPLC data previously reported.
[b] Isolated yield. In some cases, the isolated yield is lower than expected, based on the 100% conversion observed, due to co-elution of the Hantzsch pyridine by-product with products having $C^2=CO_2Me$, making the purification more challenging.
[c] % ee of crystalline product after crystallization.
[d] % ee of the mother liquor after crystallization.

(4–48 h); however, we did not observe any conversion (entry 12). Finally, based on our previous solvent screening studies,[10] this transfer hydrogenation reaction was also run using cyclohexane as the solvent (entry 13); however, only a very slight increase in enantiomeric excess was observed (entry 13). The yield and enantiomeric excess observed at the 1 mmol scale were essentially identical to those observed at the 0.2 mmol scale (entry 13).[44] To further probe the outcome observed in the transfer hydrogenation of methyl quinoline-2-carboxylate substrate **11** (with R^2=CO_2Me, R^6=H), the 6-fluoro- and 6-bromoquinoline-2-carboxylate methyl esters were also exposed to the same reaction conditions and found to give very similar outcomes (entry 13 vs. 15 and 16). Although, crystallization could be used to improve the enantiomeric purity of **8**when R^2=Me and R^6=Br (entry 3) from 80 to 93%, crystallization of **8** when R^2=CO_2Me and R^6=H, F or Br proved to be more challenging. For example, crystallization of the reaction mixture containing the methyl 6-bromo-1,2,3,4-tetrahydroquinoline-2-carboxylate (**11**, entry 16; 46% ee) led to enantiomeric enrichment of the mother liquor (rather than the crystalline material) from 46 to 66% ee (entry 16).

In summary, in this study we have identified a serious limitation in using P-chiral, N-phosphoryl sulfonamide Brønsted acids at high temperatures, due to their facile rearrangement into a racemic phosphonamidate product. Nonetheless, this class of organocatalysts leads to much faster reaction rates at nearly ambient temperature, as compared to many BINOL-based Brønsted acids, and has the ability to induce the metal- and hydrogen-gas-free transfer hydrogenation of quinolines bearing a C-2 electron-withdrawing substituent, such as an ester moiety. Although establishing a large substrate scope was beyond the purpose of this study, and the enantiomeric ratio achieved was only ca. 75:25 (*R*/*S*), it is conceivable that, upon crystallization, a significant improvement in the enantiomeric purity of product(s) would be possible.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2047-8301.

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(44) An oven-dried pressure vessel was cooled to ambient temperature in a desiccator and charged with methyl quinoline-2-carboxylate (188 mg, 1.00 mmol), Hantzsch ester (634 mg, 2.50 mmol) and **14e** (25.2 mg, 0.0501 mmol). Subsequently, anhydrous cyclohexane (5.0 mL) was added. The vial was capped, and the mixture was stirred vigorously at 50 °C for 4 h. The resulting solution was diluted with DCM (2.5 mL) and SiO_2 was added. The mixture was concentrated *in vacuo* and the crude material was first purified on Et_3N-deactvated SiO_2 by flash chromatography (0–3% EtOAc/hexanes), with the co-elution of some Hantzsch pyridine by-product. Purification by flash column chromatography on SiO_2 (0–5% EtOAc/hexanes) afforded the desired product **8** (R^2 = CO_2Me, R^6=H), as a yellow oil in 69% yield (130 mg, 0.681 mmol) and 46% ee. Chiral HPLC method: Chiralpak AD, hexane/IPA = 80:20, 1 mL/min, λ = 254 nm; t_R = 6.49 [(*R*)-, major], 7.78 [(*S*)-, minor] min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (t, *J* = 7.6 Hz, 1 H), 6.96 (d, *J* = 7.4 Hz, 1 H), 6.65 (td, *J* = 7.3, 1.2 Hz, 1 H), 6.59 (d, *J* = 8.0 Hz, 1 H), 4.36 (s, 1 H), 4.05 (dd, *J* = 8.8, 3.8 Hz, 1 H), 3.78 (s, 3 H), 2.84 (ddd, *J* = 15.1, 9.3, 5.4 Hz, 1 H), 2.75 (dt, *J* = 16.3, 5.5 Hz, 1 H), 2.29 (dtd, *J* = 13.0, 5.6, 3.8 Hz, 1 H), 2.01 (dtd, *J* = 12.9, 9.1, 5.2 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.8, 143.1, 129.3, 127.2, 120.7, 117.8, 114.7, 54.1, 52.5, 26.0, 24.8.