



Desymmetrization of malonamides via an enantioselective intramolecular Buchwald–Hartwig reaction

Lukasz Porosa, Russell D. Viirre *

Department of Chemistry and Biology, Ryerson University, 350 Victoria St., Toronto, Ontario, Canada M5B 2K3

ARTICLE INFO

Article history:

Received 22 March 2009

Revised 29 April 2009

Accepted 30 April 2009

Available online 5 May 2009

ABSTRACT

A new form of enantioselective nitrogen arylation reaction is described. Beginning with symmetrical α -(2-bromobenzyl)malonamides, intramolecular palladium-catalyzed cross-coupling using a catalyst system including 3.3 mol % Pd(OAc)₂ and 6.6 mol % of the chiral biaryl monophosphine (*R*)-MOP, desymmetrized quinolinone products are obtained in nearly quantitative yields in enantiomeric ratios up to 88:12. This Letter represents a rare example of enantioselective Buchwald–Hartwig reaction.

© 2009 Elsevier Ltd. All rights reserved.

The Buchwald–Hartwig reaction, a Pd-catalyzed cross-coupling of a nitrogen nucleophile with an aryl halide or aryl sulfonate has become a staple in organic synthesis, finding widespread application in the synthesis of natural products, medicinal agents, ligands, and materials.¹ The first reports of Pd-catalyzed (non-Sn-mediated) arylation of amines made use of P(*o*-tolyl)₃ as a supporting ligand in the catalyst system,² but it was reported shortly thereafter that chelating bisphosphines such as BINAP (**1**, Fig. 1)³ or Josiphos (**4**)⁴ provided superior results with respect to catalyst loading and substrate scope. While the chirality of the catalyst is unlikely to play a role in a typical Buchwald–Hartwig reaction (indeed, racemic ligands are often used as a cost-saving measure), the ability of these, and other chiral phosphines, to act as components of catalysts in a host of enantioselective transition metal-catalyzed transformations is well known.⁵

At first glance, there appears to be little opportunity for enantioselectivity in a reaction that forms a bond between a nitrogen atom (typically not a configurationally stable chiral center) and an sp²-hybridized carbon atom with planar geometry. It is perhaps for this reason that there have been very few reports of asymmetric Buchwald–Hartwig reactions. Nevertheless, enantioselective nitrogen arylation is theoretically possible if either (i) one enantiomer of a racemic coupling partner (either aryl halide or nitrogen nucleophile) reacts with a particular chiral catalyst faster than the other, resulting in a kinetic resolution; or (ii) the reaction was to break an element of symmetry in one of the reactants, resulting in a center, axis or plane becoming locked with a particular chiral configuration in the product.

In 1997, Rossen and Pye reported the first kinetic resolution by enantioselective Buchwald–Hartwig reaction, in which the (*S*)-isomer of racemic dibromide **10** (Fig. 2) was preferentially arylated with benzylamine using a catalyst system including (*S*)-Phanephos

(**5**) as ligand.⁶ In this example, the aminated products were not isolated, but the unreacted (*R*)-**10** was recovered in 42% resolution yield and 93% ee (i.e., 21% of the original amount of racemic **10** was recovered in enantioenriched form). In a more recent extension of this precedent, Bräse reported the resolution of racemic monobromide **11**, through diastereoselective coupling with enantiopure chiral amines such as **12**.⁷ In this case, the selectivity was dictated mainly by the chirality of **12**, but using a variety of different chiral ligands, different diastereoselectivities were observed when the opposite enantiomer of **12** was used as a coupling partner. This suggests that a particular chiral catalyst could be either matched or mismatched to react with a particular enantiomer of **12**. The resolution of racemic amines by enantioselective N-arylation has also been demonstrated, although the results to date have been poor to modest. The resolution of biaryl amines **14** and **15** using a catalyst system including (*S*)-**1** was reported to proceed in the best cases in 27% ee at 35% conversion (for **14**) and 17% ee at 45% conversion (for diarylation of **15**).⁸ The resolution of 1-(1-naphthyl)ethylamine **13** proceeded in 80% ee with 70% isolated yield using a catalyst system including (*R*)-Tol-BINAP **2**, but this result required the use of 19 equiv of the racemic amine and 8.4 equiv of a crown ether additive.⁹

In the only non-resolution-based example of enantioselective Buchwald–Hartwig reaction, Taguchi has reported that the arylation of amides of *o*-*tert*-butyl aniline **16** effectively locked out rotation about the C–N bond, resulting in a chiral axis (Fig. 3). Using a catalyst system including (*R*)-DTBM-Segphos (**6**, Fig. 1), nearly quantitative yields and enantiomeric excesses were achieved.¹⁰ Furthermore, it was shown that enolate reactions on the amide portion of the atropisomeric products proceeded with good diastereoselectivity, and this was exploited in the enantioselective synthesis of a norepinephrine transporter inhibitor.¹¹

Herein, we report a new enantioselective Buchwald–Hartwig reaction, in which a malonamide **18** (Table 1) is desymmetrized through intramolecular arylation of one of the enantiotopic

* Corresponding author. Tel.: +1 416 979 5000x4951; fax: +1 416 979 5044.
E-mail addresses: rviirre@ryerson.ca, rviirre@gmail.com (R.D. Viirre).

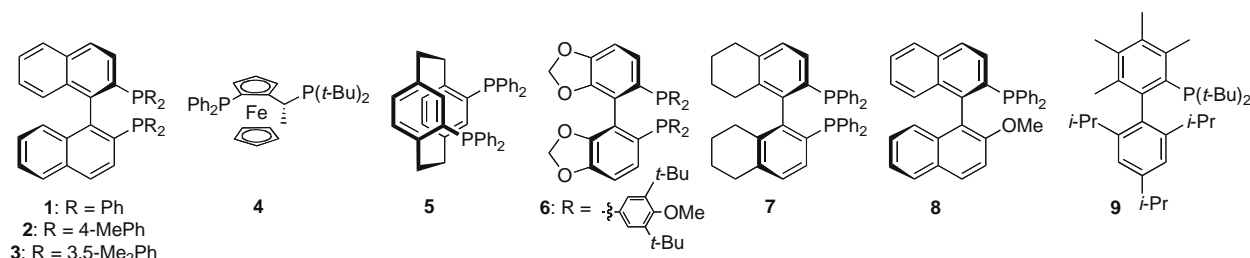


Figure 1. Phosphine ligands discussed in the text.

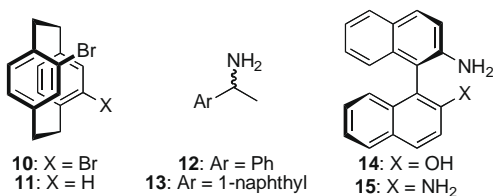


Figure 2. Substrates that have been the subject of kinetic resolution studies by enantioselective Buchwald–Hartwig reaction.

nitrogen atoms. These malonamides were readily prepared by alkylation of diethyl methylmalonate with 2-bromobenzyl bromide, followed by ester hydrolysis and amide formation all under standard conditions.¹² Before attempting any asymmetric reactions, the intramolecular arylation of the *N*-benzyl malonamide **18a** was studied using catalysts including racemic **1** as a cost-saving measure. It was found that the use of a combination of **18a**, 3.3 mol % Pd(OAc)₂, 5 mol % (*rac*)-**1**, and 1.4 equiv of Cs₂CO₃, followed by heating in toluene at 100 °C (0.1 M, sealed tube) for 24 h resulted in the formation of the desired racemic quinolinone **19a** in 85% yield. Aside from the lower concentration (0.1 vs 0.2–0.3 M), these conditions (including catalyst and base loading, and Pd/phosphine ratio) are identical to those reported by Buchwald for intramolecular arylations in achiral systems.¹³ The solubility of the substrate **18a** was found to be of some importance. The reaction proceeded smoothly when **18a** was dissolved along with the catalyst components in toluene at 100 °C ([**18a**] = 0.1 M) prior to the rapid addition of the base under a stream of argon. On the other hand, at 80 °C in the same volume of toluene, the malonamide substrate was not completely dissolved and **19a** was formed only in low yield under otherwise identical conditions. In contrast, the use of DMF as a solvent, in which **18a** was freely soluble, resulted in no reaction being observed. Toluene was therefore retained as a reaction medium for a limited screen of the effect of enantiopure ligands.

Repeating the arylation reaction under the conditions described above, but using enantiopure (*R*)-**1** as ligand, **19a** was isolated in the identical 85% yield, as expected. Analysis of the product by HPLC (Chiralcel OD-H column) revealed that the two enantiomeric products were formed in a 57:43 ratio (Table 1, entry 2).¹⁴ In an at-

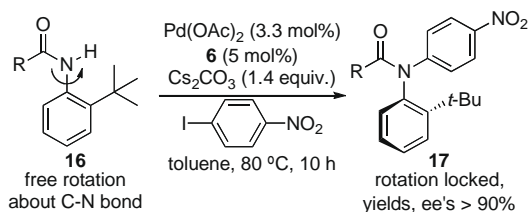
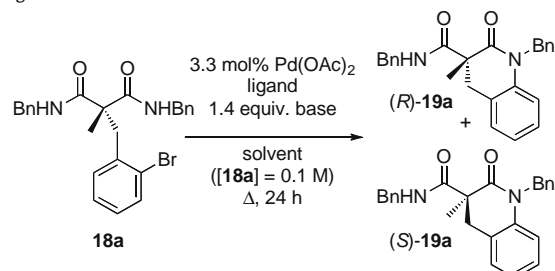


Figure 3. Taguchi's synthesis of atropisomeric anilides.

tempt to tune the steric properties of the ligand, the reaction was repeated using (*R*)-xylyl BINAP (**3**) and (*R*)-H₈-BINAP (**7**), but these were found to have detrimental effects on the yield without any enhancement of the enantiomeric ratios in the product (entries 3 and 4). The use of (*S*)-**5** or (*R*)-**6**, the ligands that had been previously successfully applied in the literature kinetic resolution⁶ and chiral axis formation¹⁰ as mentioned above, also resulted in lower yields and enantiomeric ratios compared to (*R*)-**1** (entries 5 and 6). Racemic MOP (**8**, Fig. 1) is an alternative ligand that was effective in Buchwald's intramolecular arylation reactions.¹³ This chiral biaryl monophosphine was originally developed by Hayashi, and in enantiopure form, has been successfully applied in a variety of enantioselective Pd-catalyzed reactions, notably hydrosilylations and allylations.¹⁵ When (*R*)-**8** was employed in the current reaction, the yield was comparable to **1**, but the enantioselectivity was improved significantly to a 79:21 ratio (entry 7). This markedly better ligand was therefore selected for further optimization

Table 1
Screening of reaction conditions

Entry	Ligand (mol %)	Solvent	T (°C)	Base	Yield (%)	er ^a
1	(<i>rac</i>)- 1 (5.0)	PhMe	100 ^b	Cs ₂ CO ₃	85	50:50
2	(<i>R</i>)- 1 (5.0)	PhMe	100 ^b	Cs ₂ CO ₃	85	57:43
3	(<i>R</i>)- 3 (5.0)	PhMe	100 ^b	Cs ₂ CO ₃	65	56:44
4	(<i>R</i>)- 7 (5.0)	PhMe	100 ^b	Cs ₂ CO ₃	36	56:44
5	(<i>S</i>)- 5 (5.0)	PhMe	100 ^b	Cs ₂ CO ₃	51	53:47
6	(<i>R</i>)- 6 (5.0)	PhMe	100 ^b	Cs ₂ CO ₃	62	53:47
7	(<i>R</i>)- 8 (5.0)	PhMe	100 ^b	Cs ₂ CO ₃	85	79:21
8	(<i>R</i>)- 8 (3.3)	PhMe	100 ^b	Cs ₂ CO ₃	69	74:26
9	(<i>R</i>)- 8 (6.6)	PhMe	100 ^b	Cs ₂ CO ₃	71	77:23
10	(<i>R</i>)- 8 (9.9)	PhMe	100 ^b	Cs ₂ CO ₃	59	76:24
11	(<i>R</i>)- 8 (6.6)	Dioxane	100 ^c	Cs ₂ CO ₃	96	78:22
12	(<i>R</i>)- 8 (6.6)	THF	65 ^c	Cs ₂ CO ₃	95	79:21
13	(<i>R</i>)- 8 (6.6)	MeCN	81 ^c	Cs ₂ CO ₃	14	68:32
14	(<i>R</i>)- 8 (6.6)	DMSO	100 ^b	Cs ₂ CO ₃	30	54:46
15	(<i>R</i>)- 8 (6.6)	THF	65 ^c	K ₂ CO ₃	31	83:17
16	(<i>R</i>)- 8 (6.6)	THF	65 ^c	KOt-Bu	70	85:15
17	(<i>R</i>)- 8 (6.6)	THF	65 ^c	NaOAc	25	77:23
18	(<i>R</i>)- 8 (6.6)	THF	65 ^c	NaOt-Am ^d	35	70:30
19	(<i>R</i>)- 8 (6.6)	THF	65 ^c	K ₃ PO ₄	96	79:21

^a The absolute configuration of the major enantiomer of **19a** has not been determined.

^b Reaction was heated in a sealed tube.

^c Reaction was heated at reflux temperature.

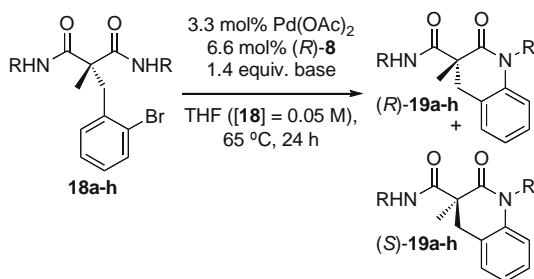
^d NaOt-Am = sodium 2-methyl-2-butoxide.

studies. Given that this monophosphine may complex palladium differently from the bisphosphines mentioned above, the ratio of Pd to (*R*)-**8** was varied from 1:1 to 1:3 (entries 8–10). While the isolated yield in the latter case was slightly lower, the enantioselectivity was nearly the same for all ratios studied.

Switching from heating in a sealed tube to heating to reflux under argon, a series of solvents were screened (Table 1, entries 11–14). In the slightly more polar ethereal solvents 1,4-dioxane or THF, the product **19a** was afforded in excellent yields and good enantiomeric ratios, however more polar solvents such as MeCN and DMSO gave inferior results. As the lower boiling THF gave the best result, a series of bases were tested in refluxing THF (entries 15–19). While potassium carbonate and potassium *t*-butoxide furnished slightly better enantiomeric ratios, these came with a sacrifice in product yield. Sodium acetate and sodium 2-methyl-2-butoxide (NaOtAm) were less competent at promoting the reaction. Potassium phosphate proved to be equal to cesium carbonate in its ability to promote the reaction in nearly quantitative yield and good enantioselectivity.

Next, the effect of the amide nitrogen substituent on the reaction outcome was evaluated. Since some of these substrates **18b–h** (Table 2) exhibited lower solubility than **18a**, these reactions were conducted at the lower concentration of 0.05 M. For most of these substrates, both K₃PO₄ and Cs₂CO₃ were employed as bases with very similar outcomes, and the better result in each case is presented in the table. In most cases, quinolinone **19** was isolated in essentially quantitative yield, with the exceptions being the more sterically demanding *N*-substituents: isopropyl (90%, entry 3), 2,6-dimethylphenyl (54%, entry 7) and 1-naphthyl (79%, entry 8).¹⁶ Among *N*-alkyl substituted malonamides, enantioselectivity increased with the steric bulk of the substituent, ranging from 69:31 er for methyl up to 85:15 er and 88:12 er for isopropyl and 4-methoxybenzyl, respectively. For *N*-aryl substrates, no trend can yet be identified, although the *N*-phenyl quinolinone was isolated with the same er as the benzyl. The er could not be determined for the naphthyl-substituted compound, since the product was isolated as an inseparable mixture of diastereomers, presumably due to torsional isomerism about the naphthyl–quinolinyl axis.¹⁷

Table 2
Effect of nitrogen substituents



Entry	Malonamide	Base	Yield (%)	er ^a
1	18b : R = Me	K ₃ PO ₄	99	69:31
2	18c : R = <i>n</i> -Bu	Cs ₂ CO ₃	99	75:25
3	18d : R = <i>i</i> -Pr	K ₃ PO ₄	90	85:15
4	18a : R = Bn	K ₃ PO ₄	99	79:21
5	18e : R = 4-methoxybenzyl	Cs ₂ CO ₃	99	88:12
6	18f : R = Ph	Cs ₂ CO ₃	99	79:21
7	18g : R = 2,6-dimethylphenyl	Cs ₂ CO ₃	54	67:33
8	18h : R = 1-naphthyl	K ₃ PO ₄	79 ^b	nd ^b

^a The absolute configuration of the major isomer of any of the quinolinone products **19a–h** has not been determined.

^b Compound **19h** was isolated as an inseparable mixture of diastereomers, due to blocked rotation about the naphthyl–quinolinyl bond.¹⁷

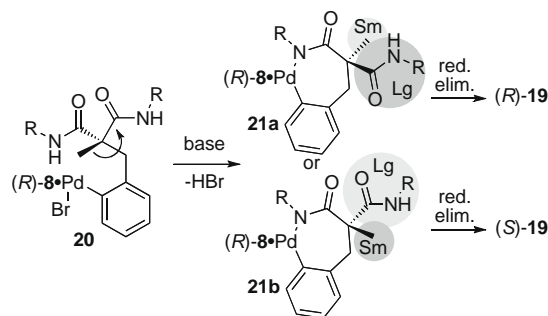


Figure 4. The proposed mechanistic step in which enantioselectivity occurs. Sm and Lg = small and large respectively.

In a study of intermolecular aryl amidation under the influence of a palladium catalyst including a biaryl monophosphine ligand such as **9** (Fig. 1), it was suggested that oxidative addition of the Pd(0) complex into the Ar–Br bond is relatively fast, with the subsequent coordination of the amide nucleophile to the Pd(II) intermediate being the turnover-limiting step.¹⁸ If it is assumed that this is also the case in the current intramolecular system, employing (*R*)-**8** (which, like **9** is a biaryl monophosphine), then oxidative addition to **18** would yield complex **20** (Fig. 4), in which the two amide groups are diastereotopic. Since **8** is capable of several different bonding modes with Pd,¹⁹ and the absolute configuration of the favored quinolinone products of these reactions currently remains unknown, it would be premature to speculate on the exact structure of intermediate **20**. Nevertheless, it could be supposed that the chiral ligand sterically impedes the rotation around the indicated bond in **20**, such that the smaller methyl group occupies a sterically demanding region in intermediate **21a** or **21b**, while the larger amide group points away from the complex. This preliminary model is supported by the observation that in most cases, the larger nitrogen substituents induce higher stereoselectivity. Work is currently underway to elaborate upon this model.

In conclusion, a new form of enantioselective Buchwald–Hartwig reaction has been developed. Enantioselection was achieved through the preferential intramolecular arylation of a prochiral nitrogen atom in a symmetrical malonamide derivative. Employing a catalyst system including 3.3 mol % Pd(OAc)₂ and 6.6 mol % (*R*)-MOP, with K₃PO₄ or Cs₂CO₃ as a base in refluxing THF, desymmetrized six-membered quinolinone derivatives were obtained in up to quantitative yields and enantiomeric ratios as high as 88:12. The C₁-symmetric biaryl monophosphine ligand provided dramatically superior enantioselectivity than a variety of C₂-symmetric bisphosphine ligands. The current methodology represents only the second example of a non-resolution-based enantioselective Buchwald–Hartwig coupling. Work is currently underway to further improve enantioselectivity and to broaden the substrate scope of the reaction, and these results will be reported in due course.

Acknowledgments

We are very grateful to the Dean of Engineering, Architecture and Science (Ryerson University) for providing start-up funding for this research program.

References and notes

- Reviews: (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361; (b) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626; (c) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041–2075.
- (a) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609–3612; (b) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348–1350.

3. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.
4. Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369–7370.
5. For a review of asymmetric arylation reactions, see: Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N. *Angew. Chem. Int. Ed.* **2001**, *40*, 3284–3308.
6. Rossen, K.; Pye, P. J.; Maliakal, A.; Volante, R. P. *J. Org. Chem.* **1997**, *62*, 6462–6463.
7. Kreis, M.; Friedmann, C. J.; Bräse, S. *Chem. Eur. J.* **2005**, *11*, 7387–7394.
8. Vyskocil, S.; Smrcina, M.; Kocovsky, P. *Tetrahedron Lett.* **1998**, *39*, 9289–9292.
9. Tagashira, J.; Imao, D.; Yamamoto, T.; Ohta, T.; Furukawa, I.; Ito, Y. *Tetrahedron: Asymmetry* **2005**, *16*, 2307–2314.
10. Preliminary report: (a) Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc.* **2005**, *127*, 3676–3677; Full paper: (b) Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923–12931.
11. Kitagawa, O.; Kurihara, D.; Tanabe, H.; Shibuya, T.; Taguchi, T. *Tetrahedron Lett.* **2008**, *49*, 471–474.
12. As a representative example, the synthesis of 2-(2-bromobenzyl)-N,N'-bis(4-methoxybenzyl)-2-methylmalonamide (**18e**) was accomplished as follows: Diethyl methylmalonate (5.10 g, 29.3 mmol) was added slowly by syringe to a suspension of NaH (60% dispersion in mineral oil, 1.30 g, 32.5 mmol) in THF (30 mL) at 0 °C, and the mixture was stirred for approximately 30 min. When hydrogen gas evolution ceased, 2-bromobenzyl bromide (9.52 g, 38.1 mmol) was added and the resulting milky white mixture was heated to reflux overnight. The solution was then cooled to room temperature, diluted with diethyl ether (60 mL), and washed with water (3 × 30 mL). The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 10% EtOAc/hexanes to afford diethyl 2-(2-bromobenzyl)-2-methylmalonate, a colorless oil, in 97% yield (9.83 g). TLC (5% EtOAc:hexanes), R_f = 0.22; ¹H NMR (CDCl₃, 400 MHz) δ 7.56–7.53 (d, J = 8.0 Hz, 1H), 7.23–7.14 (m, 2H), 7.10–7.05 (m, 1H), 4.26–4.18 (m, 4H), 3.52 (s, 2H), 1.39 (s, 3H), 1.26 (t, J = 7.0 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 171.9, 136.4, 133.1, 131.4, 128.5, 127.3, 126.3, 61.5, 55.1, 39.3, 19.4, 14.0. A portion of this diester (4.43 g, 12.9 mmol) was added to a mixture of MeOH (13 mL) and 4 M aqueous NaOH (13 mL, 52 mmol), and the mixture was heated to reflux overnight. The mixture was then cooled to room temperature, diluted with water (13 mL), and extracted with diethyl ether (1 × 13 mL). The aqueous phase was cooled to 0 °C and acidified by slow dropwise addition of 6 M HCl. The white suspension was then extracted with dichloromethane (3 × 13 mL), and the organic phase was dried over anhydrous MgSO₄ and evaporated to afford 2-(2-bromobenzyl)-2-methylmalonic acid, a white solid, in 92% yield (3.40 g), which was used without further purification. ¹H NMR (acetone-d₆, 400 MHz) δ 7.53–7.42 (m, 1H), 7.26–7.18 (m, 1H), 7.17–7.11 (m, 1H), 7.06–7.02 (m, 1H), 3.38 (s, 2H), 1.14 (s, 3H); ¹³C NMR (acetone-d₆, 100 MHz) δ 173.4, 137.7, 133.8, 132.3, 129.5, 128.4, 126.8, 55.1, 39.9, 19.6. A portion of this diacid (1.12 g, 3.9 mmol) was added to SOCl₂ (13 mL) and the mixture was heated to 60 °C for 4 h. The excess thionyl chloride was then removed by reduced pressure distillation, and the crude diacid chloride was dissolved in chloroform (40 mL). The mixture was cooled in an ice bath, and 4-methoxybenzylamine (1.25 mL, 8.6 mmol) followed by NEt₃ (1.20 mL, 8.6 mmol) was added. The mixture was removed from ice bath and heated at 60 °C overnight and then cooled to room temperature, extracted with 0.01 M HCl (4 × 20 mL), dried over MgSO₄, and evaporated under reduced pressure. The crude material was recrystallized from EtOAc to obtain the title diamide as an off-white solid in 37% yield (760 mg). Mp = 148–151 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.54–7.49 (m, 1H), 7.16–7.02 (m, 9H), 6.89–6.77 (m, 4H), 4.40–4.36 (m, 4H), 3.81 (s, 6H), 3.49 (s, 2H), 1.41 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 172.4, 159.1, 136.4, 133.0, 131.1, 129.8, 129.1, 128.4, 127.6, 126.0, 114.1, 55.3, 54.5, 43.5, 42.9, 18.4; HRMS (EI-TOF) calculated for C₂₇H₂₉BrN₂O₄ (M⁺) 524.1311; observed 524.1296.
13. Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35–37.
14. The absolute configuration of any of the quinolinone products has not yet been determined.
15. Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354–363.
16. As a representative example, the synthesis of 3-methyl-N,1-bis(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (**19e**) was accomplished as follows: A dry 10 mL round-bottomed flask was charged with Pd(OAc)₂ (1.6 mg, 0.007 mmol, 3.3 mol %), (R)-MOP (7.0 mg, 0.015 mmol, 6.6 mol %), and malonamide **18e** (116 mg, 0.22 mmol). The flask was equipped with a reflux condenser connected to an inert atmosphere manifold, and then evacuated and backfilled with Arthrice. Under a stream of Ar, anhydrous THF (4.4 mL, [malonamide] = 0.05 M) was added and the mixture was heated to reflux until the solids were dissolved. The reaction vessel was then cooled to room temperature and Cs₂CO₃ (100 mg, 0.31 mmol, 1.4 equiv) was added under a stream of Ar. The reaction mixture was heated to reflux for 24 h and then cooled to room temperature, diluted with EtOAc (15 mL), filtered through a short plug of Celite, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel eluting with 40% EtOAc:hexanes. The product **19e** was obtained as a white solid in 99% yield (99 mg). Mp = 119–122 °C; TLC (70% EtOAc:hexanes), R_f = 0.63; ¹H NMR (CDCl₃, 400 MHz) δ 7.22–7.15 (m, 1H), 7.11–7.02 (m, 2H), 7.00–6.89 (m, 5H), 6.80 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 8.5 Hz, 2H), 5.07 (d, J = 16.0 Hz, 1H), 4.91 (d, J = 16.0 Hz, 1H), 4.23–4.12 (m, 2H), 3.69 (s, 3H), 3.67 (s, 3H), 3.42 (d, J = 15.5 Hz, 1H), 2.95 (d, J = 15.5, 1H), 1.47 (s, 3H, H17); ¹³C (CDCl₃, 100 MHz) δ 172.3, 170.8, 159.0, 158.7, 138.7, 130.2, 129.0, 128.8, 128.5, 127.5, 127.3, 124.8, 123.9, 115.3, 114.2, 114.0, 55.3, 55.2, 48.7, 46.8, 43.1, 35.8, 14.2; HRMS (EI-TOF) calculated for C₂₇H₂₈N₂O₄ (M⁺) 444.2049; observed 444.2050; HPLC (Chiralcel OD-H column, eluting with 0.65 mL/min 20% *i*-PrOH:hexanes), t_R minor = 30.7 min (peak area = 4389950), t_R major = 35.7 min (peak area = 30869922), er = 12:88.
17. Evidence for torsional isomerism includes the fact that the compound appears to be a single spot by thin layer chromatography, and a single mass was observed by electron impact mass spectrometry, but ¹H NMR suggests two compounds with the same splitting patterns in a ~58:42 ratio, and HPLC analysis on Chiralcel OD-H column exhibited three peaks (presumed to be the four diastereomers, with two species co-eluting).
18. Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001–13007.
19. Kumar, P. G. A.; Dotta, P.; Hermatschweiler, R.; Pregosin, P. S. *Organometallics* **2005**, *24*, 1306–1314.