# Improved Catalysts for the Palladium-Catalyzed Synthesis of Oxindoles by Amide α-Arylation. Rate Acceleration, Use of Aryl Chloride Substrates, and a New Carbene Ligand for Asymmetric Transformations

Sunwoo Lee and John F. Hartwig*

*Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107*

*john.hartwig@yale.edu*

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Catalysts comprised $Pd(OAc)_2$ and either $PCy_3$ or sterically hindered N-heterocyclic carbene ligands provide fast rates for a palladium-catalyzed synthesis of oxindoles by amide α-arylation. This catalyst system allowed for room-temperature reactions in some cases and reactions of aryl chlorides at 70 °C. Most important, reactions occurred in high yields under mild conditions to form the quaternary carbon in α,α-disubstituted oxindoles. The combined inter- and intramolecular reaction afforded an efficient synthetic method for formation of α-aryloxindole derivatives. Surprisingly, catalysts containing *tert*-butylphosphine ligands, which have been most reactive for ketone arylations, were less active than those containing $PCy_3$. Use of new, optically active heterocyclic carbene ligands gave substantial enantioselectivity in formation of an α,α-disubstituted oxindole. In contrast, a variety of optically active phosphine ligands that were tested gave poor enantioselectivity. Mechanistic studies showed that the reaction involves rate-limiting oxidative addition of aryl halide. Base-induced formation of and reductive elimination from an arylpalladium enolate intermediate were both faster than oxidative addition. Deprotonation of the tethered amide appeared to be faster than reductive elimination of the resulting palladium enolate to form the oxindole product.

## Introduction

The palladium-catalyzed α-arylation of carbonyl compounds is emerging as a simple and useful method for conducting what has been traditionally a difficult transformation.[1−7] Electrophilic main group aryl compounds have been used in the past as an alternative method, but they are often toxic, deliver only one of several aryl groups, and require synthesis and isolation of the main group reagent.[8−10] We recently reported the palladium-catalyzed α-arylation of amides.[5] The intramolecular α-arylation of amides to form oxindoles was particularly effective, and the highest yields were observed for the synthesis of α,α-disubstituted oxindoles, which are the most difficult to construct by traditional routes. However, the reactions required high temperatures and relatively high catalyst loadings.

Oxindoles are important substructures in many biologically active molecules.[11,12] A number of methods for the synthesis of oxindoles have been reported. Friedel−Crafts cyclizations of α-haloacetanilides and variations on the Fischer indole synthesis are the classical methods of oxindole synthesis.[13] Cyclizations of 2-haloacryloylanilide derivatives by a variety of radical initiators have been reported more recently.[14−19] Metal-catalyzed routes to oxindoles include palladium-catalyzed cyclocarbonylations of 2-aminostyrenes,[20] rhodium-catalyzed carbonylations of 2-alkynylanilines,[21] rhodium- and Nafion-H-catalyzed cyclizations of α-diazoamides,[22,23] and intramolecular Heck couplings of 2-haloacryloylanilides.[24,25]

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Photochemical,[11,26] Ullmann-type,[27] and radical-promoted cyclizations of saturated 2-haloanilide derivatives[28] have also been reported.

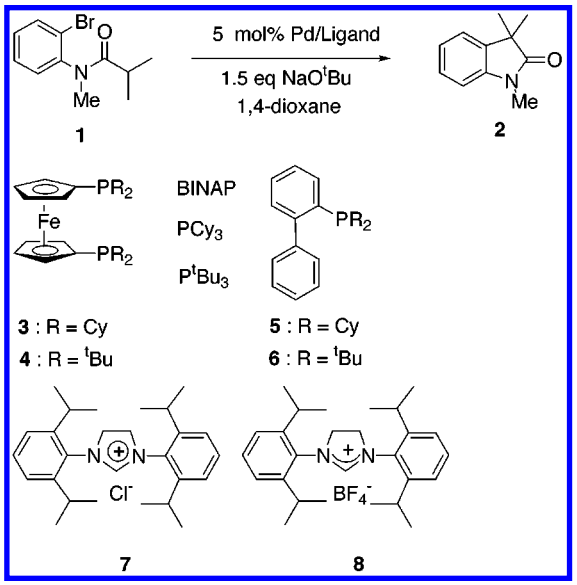
Although there are a variety of methods for synthesizing these structures, methods that form oxindoles with complete regioselectivity are rare. Friedel−Crafts methods and more recent variations do not allow control of arene regiochemistry.[13,27] Most other methodologies involve cyclization by addition of reactive intermediates to olefin or alkynyl moieties. Often, these additions occur with poor regioselectivity to produce mixtures of oxindole and 3,4-dihydroquinolin-2-one products.[1−7] One of the more attractive methods to form these structures is intramolecular Heck chemistry. However, mixtures of olefin products are often observed.[29]

The authors' laboratory and others have shown recently that the use of catalysts containing sterically hindered alkylphosphines accelerate a number of cross-coupling reactions.[6,30−41] We first showed that this class of ligand accelerates α-arylation,[6] and Buchwald's group has shown that aryldialkylphosphines can be highly reactive catalysts for ketone substrates, as well as for substrates with p$K_a$'s lower than those in ketones.[7] We were interested in using sterically hindered alkylphosphines and related heterocyclic carbene ligands to accelerate the rates for cyclizations to form oxindoles and to allow the reactions to be conducted under mild conditions. We report that the most hindered of the alkylphosphines are not effective for these reactions, but that the slightly less sterically demanding $PCy_3$ provides fast rates. In addition, we have found that heterocyclic carbene ligands generate active catalysts for these reactions, and we have designed the first optically active carbene ligand that gives substantial enantioselectivity for any transformation.

## Results and Discussion

**Cyclization of Aryl Bromide Substrates.** Tables 1 and 2 summarize our results from screening a variety of monophosphine and carbene ligands for four model substrates that undergo cyclizations to form oxindoles (eq 1). Several trends are readily apparent. First, the most general ligand for the reaction is $PCy_3$, which was not particularly effective for ketone or malonate arylations reported previously.[6] The use of this ligand allowed for lower reaction temperatures (50 °C) and catalyst loadings than previous work using BINAP as ligand.[5] The combination of Pd(0) precursors and P$^t$Bu$_3$, which were highly active for ketone arylation, did not provide mild reactions for the formation of oxindoles. Second, reactions employing sterically hindered alkyl bis-phosphines required temperatures that were similar to those published previously with BINAP[5] (Table 1, entries 2 and 3). Third, monodentate ligands were not suitable for cyclizations at an unhindered secondary C−H bond (Table 2, entries 7−12). Fourth, the optimal ligand in some cases depended on the particular substrate. For example, reaction of substrate **13** occurred in low yield when using $PCy_3$, but gave high yields when the carbene ligands **7** and **8** were used. Finally, and perhaps most important, several ligand systems were suitable for the formation of the quaternary carbon in α,α-disubstituted oxindoles. Both carbene ligands and $PCy_3$ provided high yields.

**Table 1. Effect of Ligands on Pd-Catalyzed Cyclization of Bromoanilide 1**[a]




| entry | Pd | ligand | *T* (°C) | time (h) | convn (%) | yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | $Pd(dba)_2$ | BINAP | 100 | 3 | 95 | 53 |
| 2 | $Pd(dba)_2$ | **3** | 100 | 4 | 100 | 42 |
| 3 | $Pd(dba)_2$ | **4** | 100 | 5 | 100 | 41 |
| 4 | $Pd(dba)_2$ | $PCy_3$ | 100 | 1 | 100 | 62 |
| 5 | $Pd(dba)_2$ | P$^t$Bu$_3$ | 100 | 5 | 100 | 62 |
| 6 | $Pd(dba)_2$ | $PCy_3$ | 50 | 3 | 93 | 82 |
| 7 | $Pd(OAc)_2$ | $PCy_3$ | 50 | 3 | 100 | 99 |
| 8 | $Pd(OAc)_2$ | P$^t$Bu$_3$ | 50 | 3 | 72 | 21 |
| 9 | $Pd(OAc)_2$ | **5** | 50 | 3 | 24 | 11 |
| 10 | $Pd(OAc)_2$ | **6** | 50 | 3 | 83 | 67 |
| 11 | $Pd(OAc)_2$ | **7** | 50 | 3 | 100 | 99 |
| 12 | $Pd(OAc)_2$ | **8** | 50 | 3 | 100 | 99 |

[a] Reactions run with 0.3 mmol substrate. [b] Yields determined by GC.

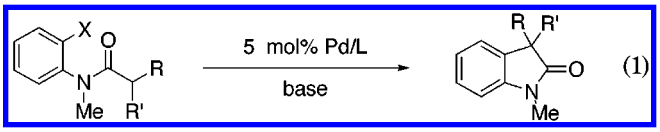


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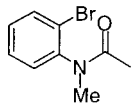
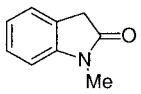
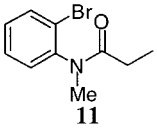
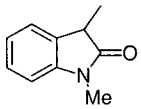
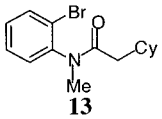
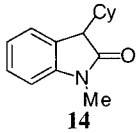
**Table 2. Optimization of Ligands on Pd-Catalyzed Cyclization of Bromoanilide**[a]

| Entry | Substrate | Product | Ligand | Conv. (%) | Yield(%)[b] | Red. Ar (%)[c] |
|---|---|---|---|---|---|---|
| 1 |  |  | $PCy_3$ | 100 | 62 | - |
| 2 | | | $P^tBu_3$ | 48 | 9 | - |
| 3 | | | **5** | 91 | 29 | - |
| 4 | | | **6** | 96 | 33 | - |
| 5 | | | **7** | 96 | 10 | - |
| 6 | **9** | **10** | **8** | 100 | 39 | - |
| 7 |  |  | $PCy_3$ | 100 | 6 | 14 |
| 8 | | | $P^tBu_3$ | 14 | 3 | trace |
| 9 | | | **5** | 100 | 14 | 14 |
| 10 | | | **6** | 89 | 10 | 12 |
| 11 | | | **7** | 100 | 11 | 15 |
| 12 | **11** | **12** | **8** | 96 | 29 | 3 |
| 13 |  |  | $PCy_3$ | 100 | 45 | 23 |
| 14 | | | $P^tBu_3$ | 41 | 34 | 4 |
| 15 | | | **5** | 44 | 31 | 4 |
| 16 | | | **6** | 66 | 36 | 7 |
| 17 | | | **7** | 92 | 56 | 9 |
| 18 | **13** | **14** | **8** | 97 | 77 | 2 |

[a] Reaction run with 0.3 mmol of substrate, 5 mol % $Pd(OAc)_2$, 5 mol % ligand, 1.5 equiv of base at 50 °C for 10 h. [b] Determined by GC after quenching with $NH_4Cl$. [c] Determined by GC/MS with authentic sample.

To find the most effective palladium precursor in the oxindole synthesis, we conducted the catalytic reaction with substrate **1** by using $Pd(dba)_2/PCy_3$ and $Pd(OAc)_2/PCy_3$. When using 5 mol % $Pd(dba)_2/PCy_3$, the reaction rate was faster than that when using 5 mol % $Pd(OAc)_2/PCy_3$, but the conversion was only 93%. When using $Pd(OAc)_2/PCy_3$, the initial reaction rate was slower than when using $Pd(dba)_2/PCy_3$, but the substrate was completely converted to product. The cause of the slow initial reaction rate catalyzed by $Pd(OAc)_2/PCy_3$ might be due to an induction period for the conversion of Pd(II) to Pd(0).

Table 3 summarizes the scope of the reaction with the ligand that provides the highest yield for each substrate. The functional group compatibility and potential electronic dependence of the reaction were evaluated with the substrates in entries 7 and 8. Reactions of substrates with electronically varied aryl groups, although a small set, showed good yields in all cases. The effect of heteroatom substitution α to the carbonyl was evaluated with oxygen substituents. Reactions with cyclic ethers occurred smoothly when using $PCy_3$ as catalyst (Table 3, entry 16). However, reaction of phenoxy-substituted system **37** did not occur, even at high temperatures. In previous work, reactions of substrates with α-aryl groups occurred more slowly than those with purely aliphatic groups when using BINAP as ligand.[5] However, cyclization of substrates with α-aryl groups occurred rapidly when using $PCy_3$. This reaction also occurred in good yield for substrates with an α-aryl group and secondary α-C−H bonds (Table 3, entry 5). One might predict this result because the lack of *β*-hydrogens in the presumed intermediate enolate complex prevents *β*-hydrogen elimination as a competing pathway. However, the absence of this reaction does not appear to distinguish the reactivity of one substrate from another. The major side product that is formed from reaction of substrate **11**, which does not contain an α-aryl group and could undergo *β*-hydrogen elimination, is simply the hydrodehalogenation product; no hydrodehalogenation product containing the expected α,*β*-unsaturated carbonyl group from *β*-hydrogen elimination was observed. The origin of the hydrogen in these cases is unclear.

**Cyclization of Aryl Chloride Substrates.** The successful use of alkylphosphines led us to evaluate cyclizations of chloroarene substrates. The substrates for cyclizations in these cases are derived from inexpensive chloroanilines. Traditionally, chloroarenes have required high temperatures for oxidative addition, but the use of sterically hindered alkylphosphines and heterocyclic carbene ligands has now allowed for reactions of chloroarene substrates under mild conditions.[7,31,32,35,39,40,42−46] Table 4 summarizes our results for oxindole synthesis using this class of substrate. The chloroarene substrates reacted at 70 °C to form oxindoles in good yields. These temperatures and the catalyst loadings are lower than those required for previous reactions of even bromoarene substrates using BINAP as ligand; reaction yields are similarly high. *N*-Methyl substrates and *N*-benzyl substrates reacted at similar rates and yields.

**The Combined Intra- and Intermolecular Arylation of Amides**. The intermolecular α-arylation of amides[5] was combined with the intramolecular process to prepare 3-aryloxindoles in a simple fashion. We postulated that the intermolecular α-arylation of an acetanilide would be slower than the intramolecular α-arylation of oxindole itself. Thus, we devised a route that would utilize initial cyclization followed by intermolecular arylation of indole. Moreover, we expected that the rate of oxidative addition of a bromoarene to Pd(0) would be faster than that of a chloroarene. Thus, we sought to construct 3-aryl oxindoles in one step from simple materials by reacting bromo-substituted acetamide **9** with a chloroarene. As shown in Table 5, the process occurred in good yields when using $PCy_3$ as ligand. This yield is particularly high considering that the yield of the cyclization of substrate **9** was 62%.

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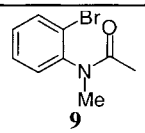
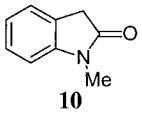
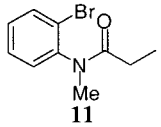
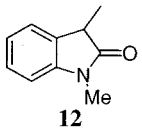
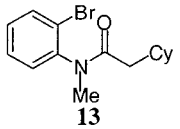
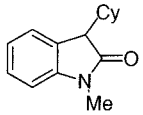
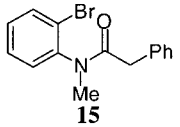
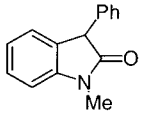
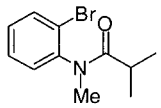
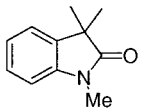
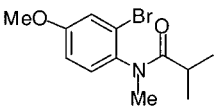
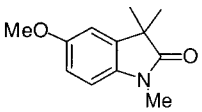
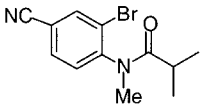
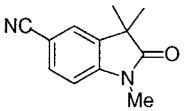
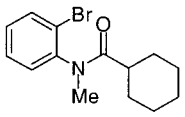
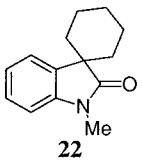
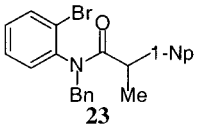
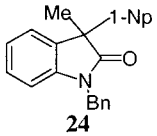
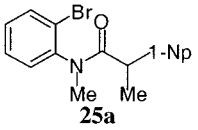
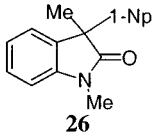
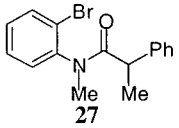
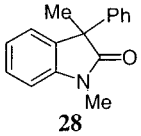
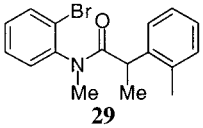
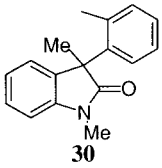
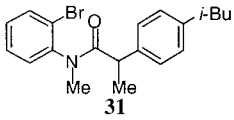
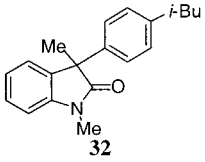
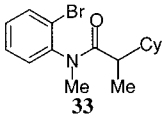
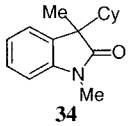
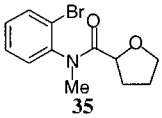
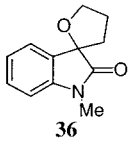
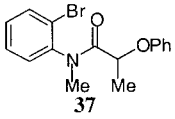
**Table 3. Formation of Oxindoles from 2-Bromoanilides**[a]

| Entry | Substrate | Product | Time[b] | Yield(%)[c] |
|---|---|---|---|---|
| 1 |  **9** |  **10** | 3 h | 62 |
| 2 |  **11** |  **12** | 3 h | 10 |
| 3 |  **13** |  **14** | 3 h<br>20 h | 43<br>75 |
| 4[d] | | | | |
| 5 |  **15** |  **16** | 1.5 h | 82 |
| 6 |  **1** |  **2** | 3 h | 92 |
| 7 |  **17** |  **18** | 4 h | 83 |
| 8 |  **19** |  **20** | 9 h | 66 |
| 9 |  **21** |  **22** | 1 h | 93 |
| 10 |  **23** |  **24** | 12 h | 97 |
| 11 |  **25a** |  **26** | 12 h | 89 |
| 12 |  **27** |  **28** | 14 h | 99 |
| 13 |  **29** |  **30** | 12 h | 99 |
| 14 |  **31** |  **32** | 14 h | 74 |
| 15 |  **33** |  **34** | 14 h | 64 |
| 16 |  **35** |  **36** | 24 h | 98 |
| 17 |  **37** | - | - | - |

[a] Reaction conditions: 5 mol % $Pd(OAc)_2$, 5 mol % $PCy_3$, 1.5 equiv of $NaO^tBu$, 1,4-dioxane (0.1 M) at 50 °C. [b] Reaction times were not optimized. [c] Isolated yields are an average of at least two runs. All compounds were fully characterized spectroscopically ($^1H$ and $^{13}C$ NMR, FTIR, and LRMS) and are consistent with previously reported values. [d] Ligand **8** was used instead of $PCy_3$.

**Asymmetric Oxindole Synthesis.** The successful formation of α,α-disubstituted oxindoles led us to seek a catalyst system for the asymmetric formation of such oxindoles. In particular, we sought formation of α-methyl, α-aryl systems that could not be formed by intramolecular Heck reactions.[29,47] Our initial studies focused on a number of different commercially available phosphine ligands, including arylphosphines. Reactions employing resolved BINAP gave enantioselectivities that were much lower than those observed for ketone arylations.[48] Even after optimization, only 46% ee was observed. Reactions with 19 different mono- and bisphosphines all provided products that showed modest enantiomeric excess or were racemic (Table 6). Only the bisphosphine **57**[49] gave significant enantioselectivity. However, slow reactions were observed in this case, even with 10 mol % catalyst. It was notable that the neomenthyl monophosphine **62** gave significant selectivity, although the selectivities were still too low for any synthetic purposes. Thus, this cyclization is difficult to conduct with good enantioselectivity and a new ligand system was necessary.

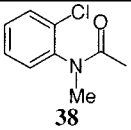
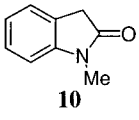
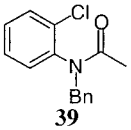
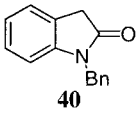
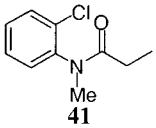
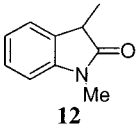
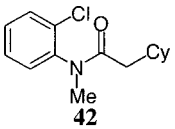
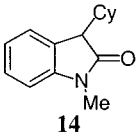
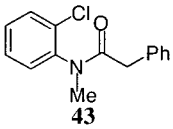
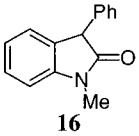
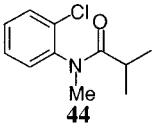
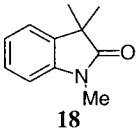
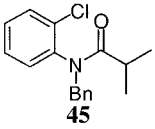
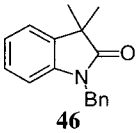
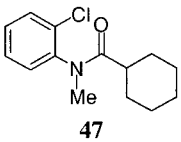
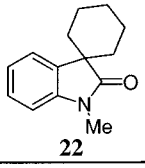
The success of carbene ligands in these reactions led us to prepare homochiral, heterocyclic carbene ligands for use in the asymmetric variant of the cyclization. We initially prepared versions of carbene **8** that contained backbone chirality. The ligand **70** in Figure 1 that contains a *trans*-diaminocyclohexane backbone was pre-

(47) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477−6487.

(48) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918−1919.

(49) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062−4066.

**Table 4. Formation of Oxindoles from 2-Chloroanilides**[a]

| Entry | Substrate | Product | Time[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1 |  **38** |  **10** | 5 h | 68 |
| 2 |  **39** |  **40** | 5 h | 64 |
| 3 |  **41** |  **12** | 24 h | 8 |
| 4 |  **42** |  **14** | 24 h | 35 |
| 5[d] | | | 24 h | 64 |
| 6 |  **43** |  **16** | 24 h | 69 |
| 7 |  **44** |  **18** | 3 h | 89 |
| 8 |  **45** |  **46** | 3 h | 93 |
| 9 |  **47** |  **22** | 4h | 90 |

[a] Reaction conditions: 5 mol % $Pd(OAc)_2$, 5 mol % $PCy_3$, 1.5 equiv of $NaO^tBu$, 1,4-dioxane (0.1 M) at 70 °C. [b] Reaction times were not optimized. [c] Isolated yields are an average of at least two runs. All compounds were fully characterized spectroscopically ($^1H$ and $^{13}C$ NMR, FTIR, and LRMS) and are consistent with previously reported values. [d] Ligand **8** was used instead of $PCy_3$.

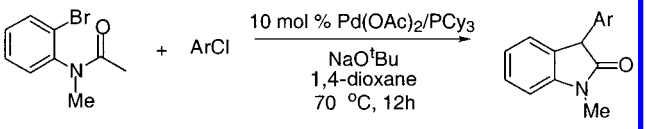
pared by modification of the standard protocol for preparation of these imidazolidine ligands.[50] Unfortunately, this ligand provided enantioselectivities that were similar to those obtained when using phosphines.

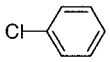
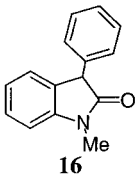
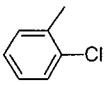
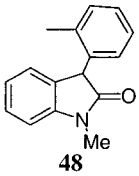
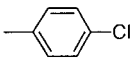
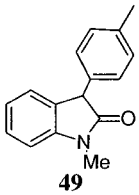
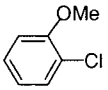
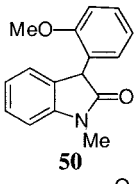
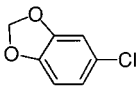
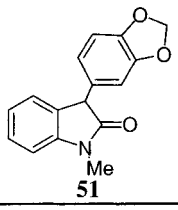
Thus, we sought a carbene with chiral substituents at nitrogen that would be readily available. Carbenes derived from phenethylamine have been prepared previously,[51] but reactions catalyzed by complexes of them showed low enantioselectivity. We felt that these ligands did not contain the appropriate steric properties to provide fast reaction rates and/or suitable transfer of chirality for the oxindole synthesis. Thus, we prepared carbene ligands **71** and **72** derived from (−)-isopinocampheylamine and (+)-bornylamine, respectively (Figure 1).

(50) Arduengo, A. J., III; Rasika Dias, H. V.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *112*, 5530−5534.

(51) Herrmann, W. A.; Goossen, L. J.; Kocher, C.; Artus, G. R. J. *Angew. Chem.* **1996**, *35*, 2805−2807.

**Table 5. Combined Intra- and Intermolecular Pd-Catalyzed Arylation of Amides**




| Entry | ArCl | Product | Yield (%)[a] |
|---|---|---|---|
| 1 |  |  **16** | 61 |
| 2 |  |  **48** | 56 |
| 3 |  |  **49** | 55 |
| 4 |  |  **50** | 60 |
| 5 |  |  **51** | 56 |

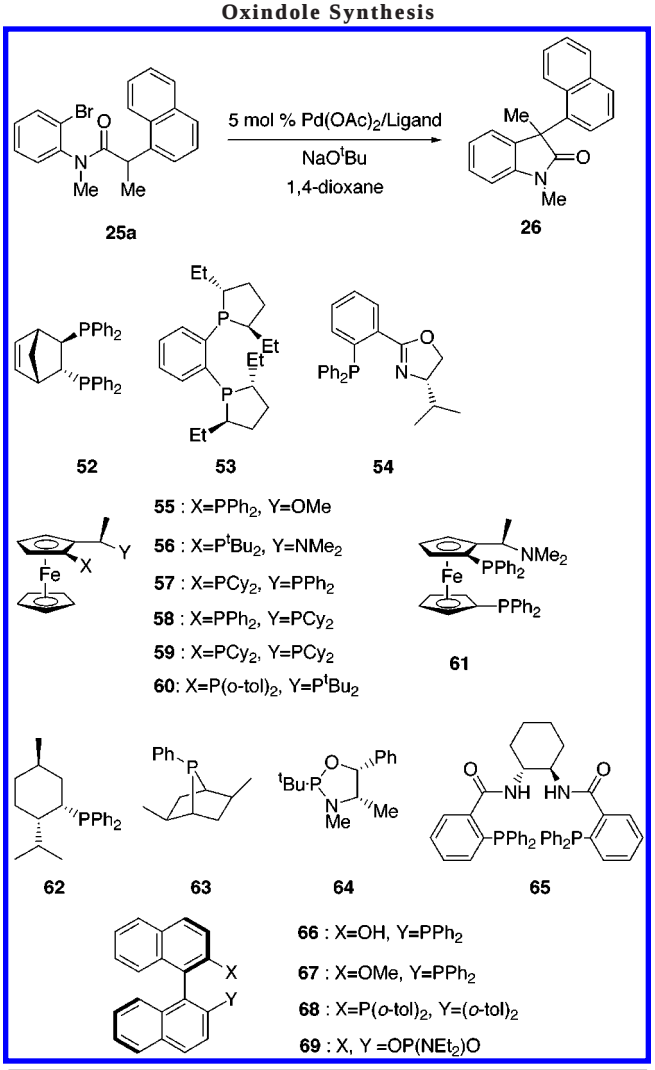
[a] Isolated yields are an average of at least two runs.

The imidazolidene ligands were again prepared readily by standard methods. The two carbene ligands that were prepared from these amines display complementary orientation of amine and α-methyl groups, potentially creating two ligands that would provide the opposite absolute stereochemistry of the oxindole product.

Reactions of the α-naphthyl, α-methyl substrate **25a** catalyzed by palladium complexes of these two ligands occurred at room temperature. Reactions using **72** were particularly rapid and allowed for enantioselective processes to be conducted below room temperature. Reactions using carbene **71** were slower than those using **72**, but still provided useful rates at 25 °C. Studies that were conducted with ligand **71** to optimize the enantioselectivity are summarized in Table 7. These experiments showed that base, counterion, and solvent were all important in controlling enantioselectivity. Ligand-to-metal ratio was not. Sodium *tert*-butoxide as base in DME solvent gave the highest selectivities.

Table 8 summarizes our results on enantioselective reactions using carbene ligands **71** and **72** using this

**Table 6. Ligand Effect of Pd-Catalyzed Asymmetric Oxindole Synthesis**




| entry | ligand | *T* (°C) | time (h) | convn[a] (%) | yield[b] (%) | % ee[c] | opt. rot.[d] |
|---|---|---|---|---|---|---|---|
| 1 | (*R*)-BINAP | 100 | 3 | 100 | 49 | 46 | (−) |
| 2 | **52** | 70 | 24 | 100 | 72 | 6 | (−) |
| 3 | **53** | 100 | 12 | 100 | 72 | 2 | (−) |
| 4 | **54** | 100 | 24 | 100 | 66 | 16 | (+) |
| 5 | **55** | 70 | 24 | 100 | 57 | 38 | (+) |
| 6 | **56** | 70 | 24 | 100 | 67 | 41 | (+) |
| 7 | **57** | 100 | 24 | 100 | 70 | 61 | (+) |
| 8 | **58** | 100 | 6 | 100 | 55 | 31 | (−) |
| 9 | **59** | 100 | 24 | 78 | 56 | 61 | (+) |
| 10 | **60** | 100 | 14 | 100 | 24 | 38 | (+) |
| 11 | **61** | 100 | 12 | 100 | 60 | 15 | (−) |
| 12 | **62** | 70 | 9 | 100 | 75 | 53 | (+) |
| 13 | **63** | 50 | 24 | 100 | 82 | 20 | (−) |
| 14 | **64** | 100 | 36 | 57 | 37 | 4 | (+) |
| 15 | **65** | 100 | 36 | 50 | 18 | 5 | (−) |
| 16 | **66** | 100 | 24 | 56 | 49 | 7 | (+) |
| 17 | **67** | 50 | 3 | 100 | 63 | 0 | 0 |
| 18 | **68** | 100 | 3 | 100 | 45 | 18 | (−) |
| 19 | **69** | 100 | 24 | 89 | 50 | 2 | (−) |

[a] Determined by GC. [b] Isolated yield after column chromatography. [c] Determined by HPLC with Chiral Daicel OD-H. [d] Measured in $CH_2Cl_2$.

solvent and base. Cyclization of **25a** using 5 mol % of a 1:1 ratio of $Pd(dba)_2$ and carbene ligand **71** as catalyst at 25 °C gave 67% ee. The analogous reaction using carbene **72** occurred with 71% enantioselectivity. However, the higher reactivity of catalysts bearing ligand **72** allowed us to conduct reactions at lower temperatures

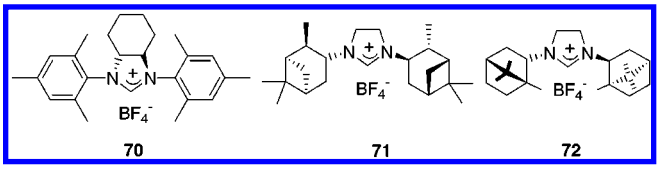



**Figure 1.** Chiral carbene ligands used for enantioselective formation of oxindoles.

**Table 7. Optimization of Palladium Source, Solvent, Temperature, and Base on Asymmetric Synthesis of Oxindole from 25a Using Ligand 71**

| entry | Pd | base | solvent | *T* (°C) | time (h) | convn[a] | yield[b] (%) | % ee[c] |
|---|---|---|---|---|---|---|---|---|
| 1[d] | $Pd(OAc)_2$ | NaO$^t$Bu | dioxane | 70 | 20 | 88 | 35 | 4 |
| 2 | $Pd(OAc)_2$ | NaO$^t$Bu | dioxane | 50 | 12 | 100 | 56 | 34 |
| 3 | $Pd(OAc)_2$ | NaO$^t$Bu | THF | 50 | 14 | 100 | 55 | 42 |
| 4 | $Pd(OAc)_2$ | NaO$^t$Bu | toluene | 50 | 14 | 100 | 50 | 34 |
| 5 | $Pd(OAc)_2$ | NaO$^t$Bu | DME | 50 | 14 | 100 | 64 | 55 |
| 6 | $Pd(OAc)_2$ | NaO$^t$Bu | diglyme | 50 | 14 | 100 | 61 | 51 |
| 7 | $Pd(OAc)_2$ | NaO$^t$Bu | *m*-xylene | 50 | 14 | 100 | 60 | 28 |
| 8 | $Pd(dba)_2$ | NaO$^t$Bu | DME | 50 | 16 | 100 | 89 | 59 |
| 9 | $Pd(dba)_2$ | KO$^t$Bu | DME | 50 | 36 | 17 | 5 | 11 |
| 10 | $Pd(dba)_2$ | LiO$^t$Bu | DME | 50 | 36 | 61 | 20 | 50 |
| 11 | $Pd(dba)_2$ | NaHMDS | DME | 50 | 14 | 100 | 56 | 48 |
| 12 | $Pd(dba)_2$ | KHMDS | DME | 50 | 16 | 100 | 57 | 6 |
| 13 | $Pd(dba)_2$ | NaO$^t$Bu | DME | 25 | 14 | 100 | 93 | 67 |

[a] Determined by GC. [b] Isolated yield. [c] Determined by HPLC with Chiral Daicel OD-H. [d] Ligand **70** used instead of ligand **71**.

and observe higher enantioselectivity. Cyclization with 10% catalyst at 10 °C gave 76% ee. As expected, the products formed from reaction of the ligands **71** and **72** displayed opposite absolute stereochemistry. These enantioselectivities are similar to those observed from intramolecular Heck reactions reported previously.[47]

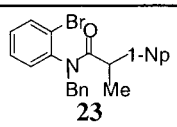
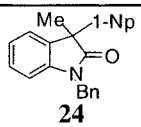
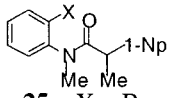
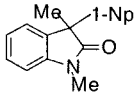
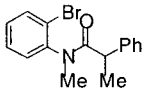
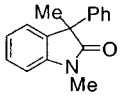
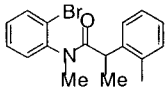
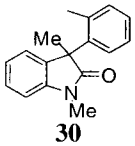
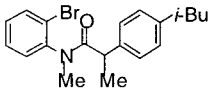
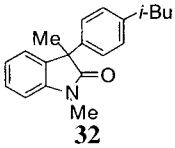
To determine if the identity of the halide influenced enantioselectivity, reactions of *N*-methyl bromide substrate **25a** were compared to those of the chloride and iodide analogues **25b** and **25c**. With both ligands, reactions of bromo-substituted **25a** occurred with similar enantioselectivity to those of chloro-substituted **25b**. These data may suggest that that the halide is not present on the complex during the enantiodiscriminating step with these substrates. However, reaction of iodo-substituted **25c** gave product that was either racemic or low in enantiomeric excess. Either the enantiodiscriminating step is different for reactions of **25c**, or the steric and electronic properties of the halide do affect the selectivity.

In many reactions, catalysts bearing monophosphines provide faster rates than those bearing bisphosphines. Thus, a long-standing problem in enantioselective catalysis is the development of chiral monophosphines that provide good selectivities.[52−54] Our results with carbene ligands **71** and **72** provide an alternative approach to this problem.

**Mechanistic Studies.** The mechanism of the cyclization reactions presumably involves oxidative addition of the aryl halide, followed by formation of an arylpalladium amide enolate intermediate and reductive elimination (Figure 2). To determine the relative rates for the different steps, we have evaluated the relative rates for

(52) Amold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865−2878.
(53) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539−11540.
(54) Reetz, M. T.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333−6336.

**Table 8. Asymmetric Oxindole Synthesis from 2-Haloanilides**

| Entry | Substrate | Product | %Pd[a]/L | Condition | Yield (%)[b] | %ee[c] |
|---|---|---|---|---|---|---|
| 1 |  **23** |  **24** | 10 %/**71** | 25 °C, 24 h | 88 | 67 |
| 2 | | | 2 %/**72** | 25 °C, 24 h | 80 | 71 |
| 3 | | | 10 %/**72** | 10 °C, 40 h | 75 | 76 |
| 4 |  **25a**; X = Br **25b**; X = Cl **25c**; X=I |  **26** | **25a** : 10 %/**71** | 50 °C, 8 h | 93 | 59 |
| 5 | | | **25b** : 10 %/**71** | 50 °C, 26 h | 91 | 69 |
| 6 | | | **25c** : 10 %/**71** | 50 °C, 6 h | 75 | 0 |
| 7 | | | **25a** : 1 %/**72** | 25 °C, 26 h | 91 | 69 |
| 8 | | | **25a** : 10 %/**72** | 0 °C, 40 h | 27 | 70 |
| 9 | | | **25b** : 10 %/**72** | 0 °C, 48 h | 5 | 58 |
| 10 | | | **25c** : 10 %/**72** | 0 °C, 36 h | 30 | 40 |
| 11 |  **27** |  **28** | 10 %/**71** | 25 °C, 24 h | 94 | 34 |
| 12 | | | 5 %/**72** | 25 °C, 24 h | 74 | 57 |
| 13 |  **29** |  **30** | 10 %/**71** | 25 °C, 24 h | 97 | 33 |
| 14 | | | 5 %/**72** | 25 °C, 24 h | 95 | 42 |
| 15 |  **31** |  **32** | 10 %/**71** | 25 °C, 24 h | 73 | 40 |
| 16 | | | 5 %/**72** | 25 °C, 20 h | 87 | 50 |

[a] $Pd(dba)_2$ was used as palladium source. [b] Isolated yield after column chromatography. [c] Determined by HPLC with Chiral Daicel OD-H.

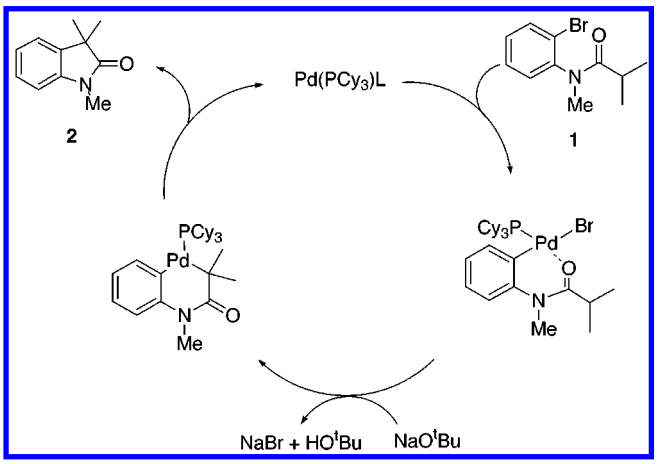
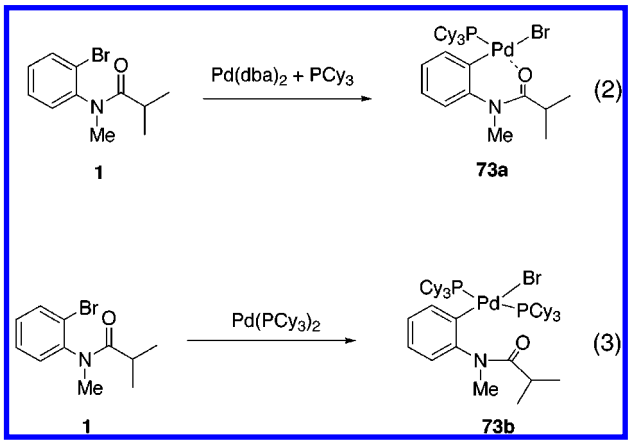



**Figure 2.** Proposed mechanism for the cyclization to form oxindoles.

stoichiometric oxidative addition of aryl halide, formation of the enolate, and reductive elimination of oxindole.

Oxidative addition of bromo isobutyramide substrate **1** occurred more rapidly to the palladium complex formed from a 1:1 ratio of $Pd(dba)_2$ than it did to $Pd(PCy_3)_2$.[55,56] Complete consumption of **1** occurred at room temperature after 20 h when reacting it with the 1:1 ratio of ligand and $Pd(dba)_2$ but required 48 h at room temperature when reacting it with $Pd(PCy_3)_2$. Moreover, the two reactions formed different products. Reaction with the 1:1 mixture formed the monophosphine complex **73a** in eq 2, while reaction with $Pd(PCy_3)_2$ formed the bisphosphine complex **73b** in eq 3. The monophosphine complex




**73a** was isolated in 60% yield, while the bisphosphine complex **73b** was obtained in 60% yield. Both compounds were characterized by standard spectroscopic methods and microanalysis. We formulate complex **73a** as a monomer with a coordinated carbonyl oxygen for several reasons. First, a similar monomeric complex was formed with P(*o*-tol)$_3$ as ligand;[57] second, the carbonyl carbon displayed $^{31}P-^{13}C$ coupling in the $^{13}C$ NMR spectrum; third, Signer solution molecular weight analysis[58] of the product yielded a molecular weight (589) that was within 10% of the calculated weight of the monomer (643).

(55) Otsuka, S.; Yoshida, T.; Matsumoto, M.; Nakatsu, K. *J. Am. Chem. Soc.* **1976**, *98*, 5850−5858.
(56) Yoshida, T.; Otsuka, S. **1985**, *28*, 113−119.
(57) Vicente, J.; Abad, J.-A.; Martinez-Vivente, E.; de Arellano, M. C. R.; Jones, P. G. *Organometallics* **2000**, *19*, 752.
(58) Signer, R. *Annalen* **1930**, *478*, 246.

To compare the rates for formation and reaction of the arylpalladium enolates, we reacted the isolated enolate complexes with NaO$^t$Bu. Reaction of arylpalladium halide complex **73a** and **73b** with NaO$^t$Bu occurred rapidly at room temperature. When monophosphine complex **73a** was treated with NaO$^t$Bu, the $^{31}$P NMR resonance of the starting complex disappeared immediately. However, the oxindole product was formed in only 20% yield at this time. From these two results one might expect to observe an arylpalladium amide complex; however, no new soluble palladium(II) phosphine complex was observed. A quantitative yield of oxindole was obtained after allowing the suspension to stand for 8 h. These results suggest that deprotonation of **73a** is rapid and that this deprotonation forms an insoluble sodium or palladium enolate that forms oxindole product over the course of 8 h. In a similar fashion, the bisphosphine palladium complex **73b** reacted rapidly with NaO$^t$Bu, but high-yield formation of oxindole (99%) required 9 h. Although slower than deprotonation, comparison of these times for formation of oxindole with those for oxidative addition of the halide substrate shows that reductive elimination of oxindole was measurably faster than the initial oxidative addition of the bromoarene substrate.

To observe the catalyst resting state and confirm that the oxidative addition is rate-determining, we monitored by $^{31}$P NMR spectroscopy reactions containing Pd(dba)$_2$/PCy$_3$ or Pd(PCy$_3$)$_2$ as catalyst. When the reaction was conducted using Pd(dba)$_2$/PCy$_3$, Pd(PCy$_3$)$_2$ ($\delta$40) was observed throughout the reaction. However, we also observed a signal at 26.3 ppm, and at the middle of the reaction time this resonance was the largest signal. As the reaction proceeded the material corresponding to this resonance at 26.3 ppm was converted to Pd(PCy$_3$)$_2$.

The same experiment using Pd(PCy$_3$)$_2$ as catalyst showed that Pd(PCy$_3$)$_2$ was the major species throughout the reaction and that the compound with a chemical shift of 26.3 ppm was absent. A minor signal at 23.6 ppm was observed, which never exceeded 20% of the palladium-phosphine complex in solution. This compound appeared to correspond to a catalyst decomposition product. It was never converted to Pd(PCy$_3$)$_2$ and did not react with PhBr added at the end of the reaction We have been unable to prepare independently a complex displaying a $^{31}$P NMR shift of 26.3 or 23.6 ppm. These complexes are not formed by adding dba to either Pd(PCy$_3$)$_2$, **73a** or **73b**. They are also not formed from reaction of Pd(dba)$_2$ and PCy$_3$ in a 1:1 ratio. This reaction, in the absence of substrate, generates a broad set of signals at 34.2−28.5 ppm.

The reason the reaction rates are faster when using a 1:1 ratio of ligand to palladium is unclear at this point, but similar observations have been made in amination, ketone arylation, and Suzuki reactions catalyzed by a 1:1 ratio of P$^t$Bu$_3$:Pd(dba)$_2$.[6,31,36] Oxidative addition to bisphosphine Pd(0) complexes containing sterically hindered ligands occurs by a preequilibrium involving ligand dissociation.[59] Thus, the generation of free phosphine retards the reaction rates for this step, which is turnover limiting. Perhaps the 1:1 ratio ensures that the concentration of free ligand remains low, even after some palladium precipitates or decomposes to a monophosphine species.

For reactions of chloro-substituted isobutyrylanilide substrate **44**, Pd(PCy$_3$)$_2$ was the major species observed by $^{31}$P NMR spectrometry when the reactions were conducted with either Pd(dba)$_2$/PCy$_3$ or Pd(PCy$_3$)$_2$ as catalyst. No resonance at 26.3 ppm was observed at any point during the reaction. Signals at 49.7, 45.6, and 40.0 ppm were observed at various times. However, Pd(PCy$_3$)$_2$ was always the major palladium−phosphine complex present in solution. These results are expected for reactions of chloroarenes and even bromoarenes when oxidative addition is the turnover-limiting step for the reaction.

**Conclusion: Effect of Ligand Properties.** It was unexpected that a less hindered alkylphosphine would provide reaction rates that are faster than those observed with the more hindered P$^t$Bu$_3$. We assume that the steric demands of the substrates for cyclization to form oxindoles accounts for this trend. A smaller Pd(0) reactive intermediate would be able to react more readily with the Ar−X linkage of a hindered substrate. Thus, it may be necessary in some cross-coupling processes to match the size of the substrate with the size of the ligand to observe the maximum rate.[60]

## Experimental Section

**General Considerations**. All coupling reactions were assembled in a drybox under nitrogen and were conducted in sealed reaction flasks. Pd(dba)$_2$,[61] **54**,[62] **63**,[63] **64**,[64] **66**,[65] and **69**,[66] were prepared by literature procedures. PCy$_3$, P$^t$Bu$_3$, **5**, **6**, (R)-BINAP, **52**, **53**, **55**−**62**, **65**, **67**, **68**, and Na$^t$OBu were obtained from commercial sources and used as received. Anhydrous grade dioxane was purchased from Aldrich and was used and stored in a nitrogen glovebox. 2-Bromo-*N*-methylaniline and 2-chloro-*N*-methylaniline were prepared from 2-bromoaniline and 2-chloroaniline, respectively.[11] 2-Chlorophenyl-*N*-methylacetamide and 2-chorophenyl-*N*-benzylacetamide were prepared according to the previously published procedures and were characterized by $^1$H and $^{13}$C NMR spectroscopy.[11] The 2-bromoanilide substrates (**23**, **25**, **27**, **29**, **31**, **33**, **35**, and **37**) displayed major and minor isomers by $^1$H and $^{13}$C NMR at room temperature due to slow rotation.[67] Naphthalene was used as a standard in quantitative GC experiments using response factors determined from isolated products. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and were uncorrected. Optical rotations were measured at 589 nm (sodium D line). Specific rotations are reported in degrees per decimeter at room temperature, and the concentration is given in grams per 100 mL of the specified solvent. $^1$H and $^{13}$C NMR data were reported in ppm downfield of TMS and were referenced to residual solvent protons or internal TMS. Low-resolution mass spectral data were obtained on a Hewlett-Packard 5890 A mass spectrometer. Electron impact ionization was used for all samples. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

**General Procedure for the Preparation of 2-Bromo-, 2-Iodo-, and 2-Chloroanilide Substrates.** 2-Bromoaniline, 2-iodoaniline, or 2-chloroaniline (1.0 equiv) was added to a mixture of the appropriate acid chloride (1.2 equiv) and triethylamine (1.5 equiv) in $CH_2Cl_2$ (0.3 M) at room temperature. The reaction was allowed to stir for 6 h. The reaction

(59) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373−5374.
(60) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.
(61) Kadin, S. B. *J. Org. Chem.* **1973**, *38*, 1349−1350.
(62) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566−568.
(63) Chen, Z.; Jiang, Q. Z., G.; Xiao, D.; Cao, P.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 4521−4523.
(64) Richter, W. J. *Chem. Ber.* **1984**, *117*, 2328−2336.
(65) Uozumi, Y.; Tanahashi, A.; Lee, S. Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945−1948.
(66) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374−2376.
(67) Siddall, T. H., III; Stewart, W. E. *J. Org. Chem.* **1969**, *34*, 2927−2933.

was then diluted with $Et_2O$ and quenched with a saturated aqueous solution of $NH_4Cl$. The organic phase was washed with a saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The resulting crude product was purified by chromatography on silica gel. The product was eluted with 20% ethyl acetate in hexanes.

***N*-(2-Bromophenyl)-*N*-methyl-2-cyclohexylpropanamide (13).** 2-Bromo-*N*-methylaniline (744 mg, 4.00 mmol) was coupled with cyclohexylacetyl chloride[68] (771 mg, 4.80 mmol) to give 1.10 g (3.55 mmol, 89%) of **13** as a white solid after chromatography. Recrystallization from hexanes gave a white solid (mp 72−73 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.61 (dd, $J$ = 7.4, 1.6 Hz, 1H), 7.32 (m, 1H), 7.18 (m, 2H), 3.12 (s, 3H), 1.81−1.73 (m, 3H), 1.63−1.52 (m, 5H), 1.17 (m, 2H), 0.97 (m, 1H), 0.68 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.75, 143.33, 134.26, 130.46, 130.01, 129.28, 123.92, 41.85, 36.14, 33.73, 33.56, 26.64, 26.54, 26.52. MS (EI): 230 ($M^+$ − Br, 100), 185 (54), 148 (75), 105 (11), 77 (14), 55 (20). Anal. Calcd for $C_{15}H_{20}BrNO$: C, 58.07; H, 6.50; N, 4.51. Found: C, 58.30; H, 6.28; N, 4.50.

***N*-Benzyl-*N*-(2-bromophenyl)-2-(1-naphthyl)propanamide (23).** 2-Bromo-*N*-benzylaniline (460 mg, 1.74 mmol) was coupled with 2-(1-naphthyl)propanoyl chloride (457 mg, 2.09 mmol) to give 540 mg (1.22 mmol, 70%) of **23** after chromatography. Recrystallization from hexanes gave a white solid (mp 99.5−100 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.74 (d, $J$ = 8.0 Hz, 1H), 7.68 (d, $J$ = 8.0 Hz, 1H), 7.62 (d, $J$ = 7.2 Hz, 1H), 7.54 (d, $J$ = 7.2 Hz, 1H), 7.41−7.17 (m, 9H), 6.85 (m, 1H), 6.26 (m, 1H), 5.83 (d, $J$ = 14.8 Hz, 0.2H), 5.71 (d, $J$ = 14.0 Hz, 0.8H), 5.56 (d, $J$ = 6.4 Hz, 1H), 4.45 (m, 0.2H), 4.20 (m, 0.8H), 4.02 (d, $J$ = 14.0 Hz, 0.8H), 3.91 (d, $J$ = 14.8 Hz, 0.2H), 1.59 (d, $J$ = 6.8 Hz, 3H). $^1$H NMR (300 MHz, 100 °C, toluene-$d_8$): $\delta$ 8.58−8.37 (br m, 3H), 7.67−7.70 (m, 11.6H), 6.74 (br s, 0.7H), 6.45 (br s, 0.7H), 6.02 (br s, 1H), 4.42−4.33 (br s, 1H), 4.12−4.01 (br s, 1H), 1.74 (br s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, M = major conformer, m = minor conformer): $\delta$ 174.64 (M), 174.41 (m), 140.49 (m), 140.34 (M), 138.98 (M), 137.78 (m), 137.69 (M), 137.27 (m), 134.50 (m), 134.38 (m), 134.26 (M), 133.76 (M), 132.56, 132.19 (m), 131.50 (m), 131.10 (M), 129.99 (M), 129.84 (M), 129.68, 129.27 (m), 129.14 (M), 128.96 (m), 128.84, 128.51 (m), 128.08 (m), 127.97 (M), 127.78 (M), 126.38, 126.14 (m), 126.08 (M), 125.89 (M), 125.59 (m), 125.01, 124.35, 122.64 (m), 122.50 (M), 52.41 (M), 52.00 (m), 40.48 (M), 39.35 (m), 21.16 (M), 21.35 (m). FTIR (KBr): 1668 cm$^{-1}$. MS (EI): 444 ($M^+$, 5), 364 (5), 217 (18), 155 (100), 128 (10), 91 (73), 65 (10), 51 (1). Anal. Calcd for $C_{26}H_{22}BrNO$: C, 70.28; H, 4.99; N, 3.15. Found: C, 70.12; H, 5.02; N, 3.04.

***N*-(2-Bromophenyl)-*N*-methyl-2-(1-naphthyl)propanamide (25a).** 2-Bromo-*N*-methylaniline (1.77 g, 9.52 mmol) was coupled with 2-(1-naphthyl)propanoyl chloride[69] (2.49 g, 11.4 mmol) to give 3.02 g (8.20 mmol, 86%) of **25a** after chromatography. Recrystallization from hexanes gave a white solid (mp 120−120.5 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.76 (d, $J$ = 8.4 Hz, 1H), 7.69 (d, $J$ = 8.4 Hz, 1H), 7.62 (d, $J$ = 8.4 Hz, 0.7H), 7.53 (d, $J$ = 7.2 Hz, 0.7H) 7.47 (d, $J$ = 7.6 Hz, 0.3H), 7.42−7.34 (m, 2.3H), 7.24−7.16 (m, 2.6H), 7.04 (m, 0.3H), 6.89 (m, 0.7H), 6.49 (t, $J$ = 7.6 Hz, 0.7H), 6.09 (d, $J$ = 8.0 Hz, 0.7H), 4.48 (quart, $J$ = 6.8 Hz, 0.3H), 4.18 (quart, $J$ = 6.8 Hz, 0.7H), 3.22 (s, 0.9H), 3.21 (s, 2.1H), 1.55 (d, $J$ = 6.8 Hz, 0.9H), 1.53 (d, $J$ = 6.8 Hz, 2.1H). $^1$H NMR (300 MHz, 100 °C, toluene-$d_8$): $\delta$ 7.69−7.62 (m, 2H), 7.54 (d, $J$ = 7.8 Hz, 0.7H), 7.36−7.02 (m, 6.2H), 6.51 (br m, 0.7H), 6.22 (br m, 0.7H), 6.02 (br m. 0.7H), 4.30 (br m, 1H), 3.12 (br s, 3H), 1.70 (br d $J$ = 8.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, M = major conformer, m = minor conformer): $\delta$ 174.76 (M), 174.69 (m), 142.78 (m), 142.33 (M), 139.13 (M), 137.38 (m), 134.58 (m), 134.38 (m), 134.28 (M), 133.87 (M), 131.47 (m), 131.22 (M), 131.10 (M), 130.63 (m), 130.00 (m), 129.85 (M), 129.29 (m), 129.21 (M), 128.71, 127.77, 126.41, 126.23, 126.16 (m), 125.89 (M), 125.60 (m), 125.10 (M), 124.73 (m), 123.93 (M), 122.66 (m), 122.57 (M), 40.23 (M), 39.25 (m), 36.94 (m), 30.89 (M), 20.96 (m), 20.67 (M). FTIR (KBr pellet): 1665 cm$^{-1}$. MS (EI): 369 (10), 367 (10), 288 (32), 212 (40), 155 (100), 128 (10), 117 (13). Anal. Calcd for $C_{20}H_{18}BrNO$: C, 65.23; H, 4.93; N, 3.80. Found: C, 65.41; H, 4.81; N, 3.72.

***N*-(2-Chlorophenyl)-*N*-methyl-2-(1-naphthyl)propanamide (25b).** 2-Chloro-*N*-methylaniline (930 mg, 3.04 mmol) was coupled with 2-(1-naphthyl)propanoyl chloride[69] (797 mg, 3.65 mmol) to give 767 mg (2.37 mmol, 78%) of **25b** after chromatography. Recrystallization from hexanes gave a white solid (mp 116−117 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.75 (d, $J$ = 8.0 Hz, 1H), 7.68 (m 1H), 7.51 (d, $J$ = 6.9 Hz, 1H), 7.45−7.31 (m, 3.3H), 7.26 (m, 1H), 7.18 (m, 1H), 7.05 (t, $J$ = 7.3 Hz, 0.3H), 6.97 (t, $J$ = 7.3 Hz, 0.7H), 6.79 (d, $J$ = 7.9 Hz, 0.3H), 6.5 (t, $J$ = 7.4 Hz, 0.7H), 6.09 (t, $J$ = 7.7 Hz, 0.7H), 4.49 (quart, $J$ = 6.7 Hz, 0.3H), 4.18 (quart, $J$ = 6.8 Hz, 0.7H), 3.21 (s, 3H), 1.54 (d, $J$ = 6.7 Hz, 0.9H), 1.53 (d, $J$ = 6.8 Hz, 2.1H). $^1$H NMR (300 MHz, 100 °C, toluene-$d_8$): $\delta$ 7.69−7.60 (m, 2H), 7.54 (d, $J$ = 8.5 Hz, 1H), 7.40 (m, 0.7H), 7.28−7.01 (m, 4.9H), 6.63 (m, 1H), 6.20 (m, 0.7H), 6.02 (m, 0.7H), 4.48 (m, 0.3H), 4.30 (m, 0.7H), 3.13 (s, 3H), 1.68 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, M = major conformer, m = minor conformer): $\delta$ 174.88 (M), 174.76 (m), 141.06 (m), 140.80 (M), 139.13 (M), 137.36 (m), 134.35 (m), 134.25, 133.23 (M), 131.26 (m), 131.16 (m), 131.10 (M), 131.05 (M), 130.65 (M), 130.46 (m), 129.80 (m), 129.63 (M), 129.19, 128.46 (m), 128.01 (M), 127.73 (M), 127.67 (m), 126.36 (M), 126.27 (m), 126.17, 126.09 (m), 125.86 (M), 125.57 (m), 125.03 (M), 122.58 (m), 122.53 (M), 40.00 (M), 39.41 (m), 36.86 (M), 36.72 (m), 20.79 (m), 20.60 (M). FTIR (KBr pellet): 1664 cm$^{-1}$. MS (EI): 323 (20), 288 (35), 168 (90), 155 (100), 128 (22), 111 (7), 77 (21), 51 (7). Anal. Calcd for $C_{20}H_{18}ClNO$: C, 74.18; H, 5.60; N, 4.33. Found: C, 74.12; H, 5.63; N, 4.29.

***N*-(2-Iodophenyl)-*N*-methyl-2-(1-naphthyl)propanamide (25c).** 2-Iodoaniline (1.00 g, 4.56 mmol) was added to the mixture of $Et_3N$ (552 mg, 15.5 mmol) and 2-(1-naphthyl)-propanoyl chloride[69] (1.20 g, 15.5 mmol) to give 1.32 g (3.28 mmol, 72%) of *N*-(2-iodophenyl)-*N*-2-(1-naphthyl)propanamide after chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.14 (dd, $J$ = 8.2, 1.0 Hz, 1H), 8.01 (d, $J$ = 8.0 Hz, 1H), 7.82 (m, 1H), 7.77 (d, $J$ = 8.2 Hz, 1H), 7.57 (d, $J$ = 7.0 Hz, 1H), 7.48−7.41 (m 4H), 7.28 (br s, 1H), 7.19 (m, 1H), 6.64 (td, $J$ = 8.6, 1.5 Hz, 1H), 4.45 (quart, $J$ = 7.2 Hz, 1H), 1.78 (d, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 173.82, 139.29, 138.68, 136.40, 134.93, 132.57, 129.74, 129.70, 129.40, 127.68, 126.83, 126,40, 126.34, 126.17, 123.99, 122.03, 89.88, 45.80, 18.20.

*N*-(2-Iodophenyl)-*N*-2-(1-naphthyl)propanamide (1.32 g, 3.28 mmol) was added to a mixture of NaH (78.7 mg, 3.28 mmol) and THF (30 mL). The resulting mixture was stirred for 12 h at room temperature. MeI (558 mg, 3.94 mmol) was then added, and the reaction was stirred for 12 h at room temperature. Saturated aqueous ammonium chloride was added, and the reaction mixture was extracted with $Et_2O$. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified by flash chromatography on silica gel to give 722 mg (1.74 mmol, 53%) of **25c**. Recrystallization from hexanes gave a white solid (mp 136−137 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.77 (dd, $J$ = 8.9, 1.3 Hz, 0.8H), 7.66 (d, $J$ = 8.2 Hz, 1H), 7.60 (d, $J$ = 8.1 Hz, 1H), 7.43 (dd, $J$ = 7.2, 0.9 Hz, 1H), 7.39 (dd, $J$ = 7.1, 1.0 Hz, 0.2H), 7.32−7.25 (m, 2.2H), 7.09−7.05 (m, 2.2H), 6.83 (td, $J$ = 7.9, 1.4 Hz, 0.2H), 6.19 (td, $J$ = 7.9, 1.6 Hz, 0.8H), 6.40 (td, $J$ = 7.7, 1.4 Hz, 0.8H), 5.97 (dd, $J$ = 7.9, 1.6 Hz, 0.8H), 4.37 (quart, $J$ = 6.9 Hz, 0.2H), 4.06 (quart, $J$ = 6.9 Hz, 0.8H), 3.12 (s, 0.6H), 3.09 (s, 2.4H), 1.45 (d, $J$ = 6.9 Hz, 2.4H), 1.44 (d, $J$ = 6.9 Hz, 0.6H). $^1$H NMR (300 MHz, 100 °C, toluene-$d_8$): $\delta$ 7.70 (d, $J$ = 7.2 Hz, 1H), 7.62 (m, 1.8H), 7.54 (d, $J$ = 8.5 Hz, 1H), 7.37 (m, 1H), 7.28−7.16 (m, 3.2H), 6.82 (m, 0.2H), 6.62 (m, 0.2H), 6.51 (m, 0.2H), 6.33 (m, 0.8H), 6.25 (m, 0.8H), 6.01 (m. 0.8H), 4.46 (m, 0.2H), 4.26 (m, 0.8H), 3.15 (s, 0.6H), 3.10 (s, 2.4H), 1.73 (d, $J$ = 6.9 Hz, 2.4H), 1.64 (d, $J$ = 6.9 Hz, 0.6H). $^{13}$C NMR (100 MHz, $CDCl_3$, M = major conformer, m = minor conformer): $\delta$ 174.44 (m), 174.24 (M), 146.18 (m), 145.41 (M), 140.93 (m), 139.92 (M), 138.79 (M), 137.23 (m), 134.33 (m), 134.05 (M), 131.53 (m), 130.88 (M), 130.24 (M), 129.95 (m),

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129.73 (m), 129.72 (m), 129.65 (M), 129.40 (M), 129.12 (m), 128.96 (M), 127.69 (m), 127.53 (M), 126.50 (m), 126.41 (m), 126.26 (M), 126.01, 125.65 (M), 125.42 (m), 124.88 (M), 122.51 (m), 122.31 (M), 100.31, 30.37 (M), 38.70 (m), 37.06 (m), 36.73 (M), 20.89 (m), 20.48 (M). FTIR (KBr pellet): 1663 $cm^{-1}$. MS (EI): 415 (10), 288 (54), 260 (50), 231 (8), 203 (7), 182 (6), 155 (100), 133 (17), 128 (19), 104 (17), 77 (16), 63 (7), 51 (7). Anal. Calcd for $C_{20}H_{18}INO$: C, 57.85; H, 4.37; N, 3.37. Found: C, 57.84; H, 4.33; N, 3.32.

***N*-(2-Bromophenyl)-*N*-methyl-2-phenylpropanamide (27).** 2-Bromo-*N*-methylaniline (1.78 g, 6.34 mmol) was coupled with 2-phenylpropanoyl chloride[70] (1.28 g, 7.61 mmol) to give 1.49 g (4.68 mmol, 74%) of **27** as a colorless oil after chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.63 (dd, $J$ = 8.0, 1.6 Hz, 0.7H), 7.49 (d, $J$ = 7.6 Hz, 0.3H), 7.35 (td, $J$ = 7.8, 1.2 Hz, 0.3H), 7.28 (dd, $J$ = 8.0, 2.0 Hz, 0.3H), 7.20−7.07 (m, 3.8H), 6.93 (m, 0.3H), 6.88 (m, 2.3H), 6.63 (dd, $J$ = 7.6, 1.6 Hz, 1H), 3.45 (quart, $J$ = 6.8 Hz, 0.3H), 3.27 (quart, $J$ = 7.2 Hz, 0.7H), 3.11 (s, 0.9H), 3.09 (s, 2.1H), 1.35 (d, $J$ = 7.2 Hz, 2.1H), 1.33 (d, $J$ = 6.8 Hz, 0.9H). $^1$H NMR (300 MHz, 100 °C, toluene-$d_8$): $\delta$ 7.32 (br s, 1H), 7.21−6.88 (br m, 5H), 6.69 (br s, 2.3H), 6.40 (br s, 0.7H), 3.44−3.34 (br s, 1H), 3.00 (s, 3H), 1.46 (d, $J$ = 8.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, M = major conformer, m = minor conformer): $\delta$ 174.58 (m), 174.39 (M), 143.09 (m), 142.85 (M), 142.28 (M), 141.21 (m), 134.65 (m), 134.18 (M), 131.49 (M), 130.72 (m), 130.39 (m), 130.33 (M), 129.31 (m), 129.10 (M), 129.02 (M), 128.83 (m), 128.66 (m), 128.07 (M), 127.39 (m), 127.32 (M), 124.84 (m), 124.30 (M), 44.68 (M), 43.90 (m), 36.83 (M), 36.81 (m), 21.29 (M), 20.75 (m). FTIR (neat, NaCl plate): 1668 $cm^{-1}$. MS (EI): 238 ($M^+$-Br, 100), 214 (25), 185 (17), 155 (4), 132 (4), 105 (100), 77 (38), 51 (10). Anal. Calcd for $C_{16}H_{16}BrNO$: C, 60.39; H, 5.07; N, 4.40. Found: C, 60.53; H, 4.93; N, 4.16.

***N*-(2-Bromophenyl)-*N*-methyl-2-(*o*-tolyl)propanamide (29).** 2-Bromo-*N*-methylaniline (1.16 g, 6.23 mmol) was coupled with 2-(*o*-tolyl)propanoyl chloride (1.36 g 7.48 mmol) to give 1.75 g (5.27 mmol, 84%) of **29** as a colorless oil after chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.59 (dd, $J$ = 8.0, 1.4 Hz, 0.8H), 7.40 (dd, $J$ = 8.1, 1.4 Hz, 0.2H), 7.34−7.30 (m, 0.4H), 7.26 (m, 0.8H), 7.14−7.00 (m, 2.2H), 6.97 (m, 1H), 6.91 (m, 0.8H), 6.83 (m, 1H), 6.03 (dd, $J$ = 11.8, 1.5 Hz, 0.8H), 3.77 (quart, $J$ = 6.8 Hz, 0.2H), 3.44 (quart, $J$ = 6.8 Hz, 0.8H), 3.13 (s, 0.6H), 3.09 (s, 2.4H), 1.41 (s, 0.6H), 1.38 (s, 2.4H), 1.26 (d, $J$ = 6.8 Hz, 3H). $^1$H NMR (300 MHz, 100 °C, toluene-$d_8$): $\delta$ 7.50 (m, 1H), 7.25 (m, 0.8H), 7.05−6.57 (m, 5.4H), 6.15 (m, 0.8H), 3.70−3.54 (m, 1H), 3.00 (s, 3H), 1.41 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, M = major conformer, m = minor conformer): $\delta$ 174.46, 142.78 (m), 142.34 (M), 140.93 (M), 139.36 (m), 135.38 (M), 135.23 (m), 134.54 (m), 133.71 (M), 131.20 (M), 130.77 (m), 130.40 (M), 130.28 (m), 129.86 (M), 129.06 (m), 128.78 (M), 128.01 (m), 126.92, 126.86, 126.77, 124.64 (m), 124.25 (M), 40.76 (M), 39.36 (m), 36.62 (m), 36.58 (M), 20.29 (m), 19.67 (M), 18.64 (m), 18.60 (M). FTIR (neat, NaCl plate): 1668 $cm^{-1}$. MS (EI): 333 (10), 331 (7), 252 (80), 212 (20), 185 (17), 155 (5), 119 (100), 91 (47), 77 (47), 51 (10). Anal. Calcd for $C_{17}H_{18}BrNO$: C, 61.46; H, 5.46; N, 4.22. Found: C, 61.67; H, 5.47; N, 3.94.

***N*-(2-Bromophenyl)-*N*-methyl-2-(4-isobutyl)phenylpropanamide (31).** 2-Bromo-*N*-methylaniline (372 mg, 2.00 mmol) was coupled with 2-(4-isobutylphenyl)propanoyl chloride[71] (571 mg 2.4 mmol) to give 531 mg (1.42 mmol, 71%) of **31** as a colorless oil after chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.72 (dd, $J$ = 8.0, 1.2 Hz, 0.7H), 7.57 (dd, $J$ = 8.0, 1.2 Hz, 0.3H), 7.44 (m, 0.3H), 7.37 (m, 0.3H), 7.26 (m, 0.3H), 7.23 (m, 0.7H), 7.16 (m, 0.7H), 6.97 (d, $J$ = 7.6 Hz, 2H), 6.89−6.85 (m, 2H), 6.71 (dd, $J$ = 7.8, 1.2 Hz, 0.7H), 3.52 (quart, $J$ = 7.2 Hz, 0.3H), 3.33 (quart, $J$ = 6.8 Hz, 0.7H), 3.20 (m, 0.9H), 3.18 (m, 2.1H), 2.43 (d, $J$ = 6.8 Hz, 1.4H), 2.40 (d, $J$ = 6.8 Hz, 0.6H), 1.82 (m, 1H), 1.42 (m, 3H), 0.91 (m, 3H), 0.89 (m, 3H). $^1$H NMR (300 MHz, 100 °C, toluene-$d_8$): $\delta$ 7.48 (br m, 1H), 7.06−6.94 (br m, 4H), 6.78 (br m, 2H), 6.54 (br s, 1H), 3.53−3.42 (br s, 1H), 3.11 (s, 3H), 2.41 (d, $J$ = 6.9 Hz, 2H), 1.84 (sept, $J$ = 6.6 Hz, 1H), 1.58 (br s, 3H), 0.93 (d, $J$ = 6.6 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, M = major conformer, m = minor conformer): $\delta$ 174.76 (m), 174.64 (M), 143.15 (m), 142.80 (M), 140.69, 139.55 (M), 138.40 (m), 134.64 (m), 134.12 (M), 131.60 (M), 130.77 (m), 130.31 (m), 130.26 (M), 129.75 (M), 129.61 (m), 129.23 (m), 129.04 (M), 128.28 (m), 127.77 (M), 124.93 (m), 124.32 (M), 45.69 (m), 45.63 (M), 44.37 (M), 43.62 (m), 36.84 (M), 36.81 (m), 30.87 (m), 30.85 (M), 23.08 (m), 23.05 (M), 22.98, 21.25 (M), 20.76 (m). FTIR (neat, NaCl plate): 1669 $cm^{-1}$. MS (EI): 294 ($M^+$ − Br, 100), 212 (40), 188 (10), 161 (10), 145 (12), 117 (40), 91 (32), 77 (20), 57 (5). Anal. Calcd for $C_{20}H_{24}BrNO$: C, 64.18; H, 6.46; N, 3.74. Found: C, 64.44; H, 6.41; N, 3.81.

***N*-(2-Bromophenyl)-*N*-methyl-2-cyclohexylpropanamide (33).** 2-Bromo-*N*-methylaniline (1.21 g, 6.51 mmol) was coupled with 2-cyclohexylpropanoyl chloride[72] (1.36 g 7.81 mmol) to give 1.93 g (5.96 mmol, 92%) of **33** as a colorless oil after chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.67 (m, 1H), 7.38 (m, 1H), 7.26 (m, 2H), 3.20 (d, $J$ = 1.2 Hz, 1.7H),3.19 (d, $J$ = 1.2 Hz, 1.3H), 1.84 (m, 1H), 1.76−1.49 (m, 6H), 1.26−1.13 (m, 2H), 1.08 (dd, $J$ = 6.8, 0.8 Hz, 1.7H), 1.04 (m, 1H), 1.03 (dd, $J$ = 6.8, 0.8 Hz, 1.3H), 0.84 (m, 1H), 0.66 (m, 1H). $^1$H NMR (300 MHz, 100 °C, toluene-$d_8$): $\delta$ 7.40 (d, $J$ = 8.0 Hz, 1H), 7.06−6.96 (br m, 2H), 6.77 (m, 1H), 3.15 (s, 3H), 2.05 (br s, 1H), 1.82−1.62 (m, 6H), 1.25−1.13 (br m, 7H), 0.81 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, M = major conformer, m = minor conformer): $\delta$ 177.54 (m), 177.33 (M), 143.55 (M), 143.46 (m), 134.73 (m), 134.51 (M), 131.36, 130.46 (m), 130.16 (M), 129.26 (M), 129.22 (m), 124.13 (M), 123.60 (m), 43.59 (m), 43.42 (M), 42.12 (M), 40.98 (m), 36.54 (M), 36.46 (m), 33.23 (m), 32.78 (M), 30.26 (M), 30.05 (m), 27.09 (M), 27.03 (m), 27.00, 26.92, 16.21 (m), 16.03 (M). FTIR (neat, NaCl plate): 1661 $cm^{-1}$. MS (EI): 244 ($M^+$ − Br, 100), 185 (50), 162 (100), 147 (5), 111 (59), 69 (75), 55 (41). Anal. Calcd for $C_{16}H_{22}BrNO$: C, 59.27; H, 6.84; N, 4.32. Found: C, 59.19; H, 6.95; N, 4.26.

***N*-(2-Bromophenyl)-*N*-methyltetrahydro-2-furancaboxamide (35).** 2-Bromoaniline (3.01 g, 17.5 mmol) was added to the mixture of DCC (4.33 g, 21.0 mmol) and tetrahydro-2-furancarboxylic acid (2.44 g, 21.0 mmol) in DMF (80 mL) at room temperature. The resulting solution was allowed to stir for 12 h. The reaction mixture was poured into water and extracted with $Et_2O$. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The resulting crude product was purified by flash chromatography on silica gel to give 1.95 g (41%) of *N*-(2-bromophenyl)tetrahydro-2-furancaboxamide. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 9.17 (br s, 1H), 8.41 (m, 1H), 7.54 (m, 1H), 7.31 (m, 1H), 7.00 (m, 1H), 4.51 (m, 1H), 4.13 (m, 1H), 4.00 (m, 1H), 2.35 (m, 1H), 2.20 (m, 1H), 1.98 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 172.52, 135.88, 132.95, 129.02, 125.80, 122.02, 114.28, 79.48, 70.54, 31.00, 26.22.

*N*-(2-Bromophenyl)tetrahydro-2-furancaboxamide (1.78 g, 6.59 mmol) was added to a mixture of NaH (237 mg, 9.88 mmol) and THF (40 mL). The resulting mixture was stirred for 12 h at room temperature. MeI (0.82 mL, 13.2 mmol) was then added, and the reaction was stirred for 12 h at room temperature. Saturated aqueous ammonium chloride was added, and the reaction mixture was extracted with $Et_2O$. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified by flash chromatography on silica gel to give 1.37 g (4.82 mmol, 73%) of **35**, which was obtained as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.67 (m, 1H), 7.37 (m, 2H), 7.25 (m, 1H), 4.14 (m, 0.6H), 4.11 (m, 0.4H), 4.03−3.93 (m, 1H), 3.76 (m, 1H), 3.19 (s, 3H), 2.14−1.92 (m, 2H), 1.86−1.68 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 173.74 (m), 172.97 (M), 142.56 (M), 142.42 (m), 134.58 (m), 134.29 (M), 131.06, 130.77 (m), 130.48 (M), 129.58 (m), 129.32 (M), 124.33 (m), 123.80 (M), 76.23 (m), 75.59 (M), 70.28 (m), 69.94 (M), 36.83, 31.13

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(m), 30.05 (M), 26.68 (M), 26.33 (m). FTIR (neat, NaCl plate): 1674 $cm^{-1}$. MS (EI): 285 (1), 283 (1), 204 (35), 176 (40), 71 (100). Anal. Calcd for $C_{12}H_{14}BrNO_2$: C, 50.72; H, 4.97; N, 4.93. Found: C, 51.00; H, 5.14; N, 5.19.

***N*-(2-Bromophenyl)-*N*-methyl-2-phenoxypropanamide (37).** 2-Bromo-*N*-methylaniline (730 mg, 3.92 mmol) was coupled with 2-phenoxypropanoyl chloride (868 mg 4.70 mmol) to give 1.07 g (3.20 mmol, 82%) of **37** as a colorless oil after chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.56 (m, 1H), 7.25 (m, 0.4H), 7.16−7.04 (m, 5H), 6.93 (m, 0.4H), 6.84 (m, 0.6H), 6.69 (d, $J$ = 8.0 Hz, 0.6H), 6.56 (d, $J$ = 7.6 Hz, 1H), 4.54 (quart, $J$ = 6.8 Hz, 0.4H), 4.50 (quart, $J$ = 6.4 Hz, 0.6H), 3.17 (s, 1.2H), 3.16 (s, 1.8H), 1.38 (d, $J$ = 6.8 Hz, 1.2H), 1.37 (d, $J$ = 6.4 Hz, 1.8H). $^1$H NMR (300 MHz, 100 °C, toluene-$d_8$): $\delta$ 7.36−7.30 (m, 2H), 7.20 (m, 2H), 6.94−6.82 (m, 3H), 6.75−6.63 (m, 2H), 4.73 (br s, 1H), 3.18 (s, 3H), 1.57 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, M = major conformer, m = minor conformer): $\delta$ 171.67 (m), 171.00 (M), 157.68 (m), 157.63 (M), 142.07, 134.70 (m), 134.37 (M), 131.16, 130.57 (M), 130.54 (m), 129.98 (M), 129.89 (m), 129.49 (M), 129.22 (m), 123.95 (m), 123.63 (M), 122.36 (M), 122.14 (m), 116.99 (M), 116.76 (m), 72.84 (m), 72.40 (M), 37.47 (m), 37.07 (M), 18.66 (m), 17.72 (M). FTIR (neat, NaCl plate): 1678 $cm^{-1}$. MS (EI): 335 (2), 333 (2), 254 ($M^+$ − Br, 25), 211 (25), 184 (20), 161 (50), 146 (15), 121 (100), 93 (20), 77 (76), 51 (26). Anal. Calcd for $C_{16}H_{16}BrNO_2$: C, 57.50; H, 4.83; N, 4.19. Found: C, 57.44; H, 4.86; N, 4.19.

***N*-(2-Chlorophenyl)-*N*-methylpropanamide (41).**[11] 2-Chloro-*N*-methylaniline (980 mg, 6.95 mmol) was coupled with propionyl chloride (771 mg 8.34 mmol) to give 1.25 g (6.34 mmol, 91%) of **41** as colorless oil after chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.35 (m, 1H), 7.18 (m, 2H), 7.12 (m, 1H), 3.05 (s, 3H), 1.82 (quart, $J$ = 7.6 Hz, 2H), 0.89 (t, $J$ = 7.6 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 174.39, 141.80, 133.61, 131.25, 130.41, 130.08, 128.87, 36.31, 27.74, 9.97. MS (EI): 162 ($M^+$ − Cl, 100), 141 (100), 111 (20), 90 (10), 77 (55), 57 (43), 51 (14).

***N*-(2-Chlorophenyl)-*N*-methylcyclohexylacetamide (42).** 2-Chloro-*N*-methylaniline (1.10 g, 7.80 mmol) was coupled with cyclohexylacetyl chloride (1.50 g, 9.34 mmol) to give 1.93 g (7.28 mmol, 93%) of **42** as a colorless oil after chromatography. Recrystallization from hexanes gave a white solid (mp 74−75 °C). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.51 (m, 1H), 7.33 (m, 2H), 7.26 (m, 1H), 3.20 (s, 3H), 1.85 (m, 2H), 1.69 (m, 6H), 1.23 (m, 2H), 1.18 (m, 1H), 0.76 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 172.57, 141.51, 133.13, 130.71, 130.07, 129.44, 128.20, 41.33, 35.78, 34.84, 33.31, 33.21, 26.29, 26.19, 26.16. FTIR (KBr): 1666 $cm^{-1}$. MS (EI), 230 ($M^+$-Cl, 100), 183 (50), 168 (10), 148 (100), 141 (100), 125 (10), 111 (10), 97 (35), 77 (47), 67 (9), 55 (80). Anal. Calcd for $C_{15}H_{20}ClNO$: C, 67.79; H, 7.58; N, 5.27. Found: C, 67.81; H, 7.76; N, 5.17.

***N*-(2-Chlorophenyl)-*N*-methylphenylacetamide (43).**[11] 2-Chloro-*N*-methylaniline (1.02 g, 7.23 mmol) was coupled with phenylacetyl chloride (1.34 g 8.68 mmol) to give 1.12 g (4.32 mmol, 60%) of **43** as a colorless oil after chromatography.$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.42 (dd, $J$ = 7.6, 1.6 Hz, 1H), 7.27−7.19 (m, 2H), 7.15−7.10 (m, 3H), 7.07 (dd, $J$ = 7.6, 2.0 Hz, 1H), 6.95 (m, 2H), 3.35 (d, $J$ = 14.8 Hz, 1H), 3.24 (d, $J$ = 14.8 Hz, 1H), 3.13 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 171.60, 141.60, 135.52, 133.77, 131.28, 130.86, 130.29, 129.78, 128.88, 128.75, 127.24, 41.57, 36.69. MS (EI): 224 ($M^+$ − Cl, 100), 168 (18), 141 (63), 91 (70), 77 (18), 51 (7).

***N*-(2-Chlorophenyl)-*N*-methyl-2-methylpropanamide (44).**[11] 2-Chloro-*N*-methylaniline (758 mg, 5.38 mmol) was coupled with isobutyryl chloride (688 mg, 6.46 mmol) to give 1.09 g (5.17 mmol, 96%) of **44** as colorless oil after chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.43 (m, 1H), 7.27 (m, 2H), 7.20 (m, 1H), 3.12 (s, 3H), 2.21 (sept, $J$ = 6.8 Hz, 1H), 0.98 (d, $J$ = 6.8 Hz, 3H), 0.93 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 178.09, 141.96, 133.70, 131.30, 130.32, 130.03, 128.82, 36.48, 32.11, 20.51, 19.97. MS (EI): 176 ($M^+$ − Cl, 100), 141 (68), 111 (5), 77 (20), 51 (5).

***N*-Benzyl-*N*-(2-chlorophenyl)-2-methylpropanamide (45).**[11] 2-Chloro-*N*-benzylaniline (820 mg, 3.78 mmol) was coupled with isobutyryl chloride (483 mg, 4.53 mmol) to give 1.05 g (3.66 mmol, 97%) of **45** after chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.41 (dd, $J$ = 8.0, 1.2 Hz, 1H), 7.21−7.15 (m, 4H), 7.11−7.09 (m, 2H), 7.05 (ddd, $J$ = 7.8, 7.6, 1.6 Hz, 1H), 6.72 (dd, $J$ = 7.6, 1.2 Hz, 1H), 5.52 (d, $J$ = 14.0 Hz, 1H), 3.96 (d, $J$ = 14.0 Hz, 1H), 2.18 (sept, $J$ = 6.8 Hz, 1H), 1.03 (d, $J$ = 6.8 Hz, 3H), 0.94 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 178.02, 139.98, 137.94, 133.98, 131.70, 131.22, 130.04, 129.77, 128.99, 128.17, 128.04, 51.95, 34.43, 20.70, 19.89. MS (EI): 287 ($M^+$, 10), 252 ($M^+$ − Cl, 100), 217 (50), 180 (10), 152 (7), 138 (11), 91 (100), 65 (8), 51 (5).

***N*-(2-Chlorophenyl)-*N*-methylcyclohexanecarbamide (47).** 2-Chloro-*N*-methylaniline (789 mg, 5.60 mmol) was coupled with cyclohexylcarbonyl chloride (985 mg, 6.72 mmol) to give 1.26 g (5.01 mmol, 89%) of **47**. Recrystallization from hexanes gave a white solid (mp 87−88 °C). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.52 (m, 1H), 7.34 (m, 2H), 7.27 (m, 1H), 3.18 (s, 3H), 1.95 (m, 1H), 1.74−1.44 (m, 8H), 1.20 (m, 1H), 0.97 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 176.51, 141.51, 133.17, 130.73, 129.76, 129.42, 128.20, 41.91, 35.38, 29.78, 29.06, 25.69, 25.64, 25.46. FTIR (KBr): 1663 $cm^{-1}$. MS (EI): 216 ($M^+$ − Cl, 80), 141 (100), 83 (90), 55 (70). Anal. Calcd for $C_{14}H_{18}ClNO$: C, 66.79; H, 7.21; N, 5.56. Found: C, 66.68; H, 7.09; N, 5.36.

**General Procedure for the Synthesis of Oxindoles from 2-Bromoanilide or 2-Chloroanilide Substrates Using $PCy_3$ or Ligand 8.** In the drybox, $Pd(OAc)_2$ (11.2 mg, 0.0500 mmol), $PCy_3$ (14.0 mg, 0.0500 mmol), or carbene ligand **8** (23.9 mg, 0.0500 mmol) was combined with NaO$^t$Bu (144 mg, 1.50 mmol) in a small round-bottom flask. 1,4-Dioxane (10 mL) was added, and the flask was sealed with a septum. The resulting mixture was allowed to stir for 1 min, at which time the 2-bromo or 2-chloroanilide substrate was added. After being removed from the drybox, the flask was placed in an oil bath at the appropriate temperature (see Tables 3 and 4) until the starting material was consumed, as determined by GC and TLC. The reaction was poured into 20 mL of saturated aqueous ammonium chloride and extracted (3 × 20 mL) with $Et_2O$. The combined ether extracts were washed with brine (60 mL), dried over $MgSO_4$, and filtered. The solvent was removed under vacuum, and the resulting crude product was purified by flash chromatography on silica gel. The product was eluted with 15% ethyl acetate in hexanes. The products (**2**, **10**, **12**, **16**, **18**, **20**, **22**, and **40**) were characterized by comparison of their $^1$H NMR and $^{13}$C NMR spectra to those reported previously; their purity was confirmed by GC analysis.[5]

**1-Benzyl-3-(1-naphthyl)-3-methyloxindole (24).** Substrate **23** (133 mg, 0.300 mmol), $Pd(OAc)_2$ (3.3 mg, 0.015 mmol), $PCy_3$ (4.2 mg, 0.015 mmol), and NaO$^t$Bu (43.2 mg, 0.450 mmol) were used. Reaction at 50 °C for 12 h gave 98 mg (90%) of **24** after silica gel chromatography. Recrystallization from hexanes gave a white solid (mp 142−143.5 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.77 (d, $J$ = 7.6 Hz, 1H), 7.73 (d, $J$ = 8.0 Hz, 1H), 7.69 (d, $J$ = 8.0 Hz, 1H), 7.43 (m, 3H), 7.30−7.19 (m, 4H), 7.09 (dd, $J$ = 8.0, 7.6 Hz, 1H), 6.91 (d, $J$ = 7.6 Hz, 1H), 6.86 (dd, $J$ = 7.8, 7.2 Hz, 1H), 6.79−6.70 (m, 3H), 5.12 (d, $J$ = 15.2 Hz, 1H), 4.88 (d, $J$ = 15.2 Hz, 1H), 1.85 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 180.78, 141.71, 137.22, 136.52, 135.53, 134.80, 131.76, 129.62, 129.46, 129.30, 128.78, 128.35, 128.21, 126.79, 126.62, 125.77, 125.54, 124.48, 123, 53, 123.37, 110.06, 52.92, 44.78, 27.54. FTIR (KBr): 1715 $cm^{-1}$. MS (EI): 363 ($M^+$, 64), 272 (100), 254 (22), 215 (20), 153 (10), 116 (55), 91 (80), 65 (12). Anal. Calcd for $C_{26}H_{21}NO$: C, 85.92; H, 5.82; N,3.85. Found: C, 85.68; H, 6.05; N, 3.77.

**1,3-Dimethyl-3-(1-naphthyl)oxindole (26).** Substrate **25a** (184 mg, 0.500 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $PCy_3$ (7.0 mg, 0.025 mmol), and NaO$^t$Bu (72.0 mg, 0.750 mmol) were used. Reaction at 50 °C for 12 h gave 139 mg (97%) of **26** after silica gel chromatography. Recrystallization from hexanes gave a white solid (mp 127−128 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.91 (d, $J$ = 7.2 Hz, 1H), 7.87 (d, $J$ = 8.4 Hz, 1H), 7.84 (d, $J$ = 8.0 Hz, 1H), 7.60 (dd, $J$ = 7.8, 7.6 Hz, 1H), 7.35 (m, 2H), 7.21 (m, 1H), 7.08 (d, $J$ = 7.6 Hz, 1H), 6.96 (m, 2H), 6.87 (d, $J$ = 7.2 Hz, 1H), 3.48 (s, 3H), 1.96 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 180.97, 142.65, 137.19, 135.57, 134.85, 131.82,

129.64, 129.56, 128.41, 126.79, 126.77, 125.75, 125.59, 123.96, 123.59, 123.33, 109.13, 52.96, 27.33, 27.21. FTIR (KBr): 1716 $cm^{-1}$. MS (EI): 287 ($M^+$, 100), 262 (69), 256 (7), 244 (20), 215 (20), 202 (10), 160 (9), 127 (7), 101 (6), 77 (6). Anal. Calcd for $C_{20}H_{17}NO$: C, 83.60; H, 5.96; N, 4.87. Found: C, 83.46; H, 5.77; N, 4.77.

**1,3-Dimethyl-3-phenyloxindole (28).** Substrate **27** (159 mg, 0.500 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $PCy_3$ (7.0 mg, 0.025 mmol), and NaO$^t$Bu (72.0 mg, 0.750 mmol) were used. Reaction at 50 °C for 14 h gave 118 mg (99%) of **28** as a colorless oil after silica gel chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.26−7.20 (m, 5H), 7.16 (m, 1H), 7.10 (m, 1H), 7.01 (ddd, $J$ = 7.6, 6.4, 1.2 Hz, 1H), 6.83 (d, $J$ = 7.6 Hz, 1H), 3.15 (s, 3H), 1.71 (s, 3H). $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta$ 180.06, 143.83, 141.39, 135.42, 129.16, 128.73, 127.85, 127.26, 124.81, 123.41, 108.93, 52.76, 27.11, 24.37. FTIR (neat, NaCl plate): 1716 $cm^{-1}$. MS (EI): 237 ($M^+$, 93), 222 (100), 207 (10), 194 (15), 178 (7), 165 (10), 152 (8), 130 (4), 117 (5), 102 (2), 91 (4), 77 (5), 51 (4). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.75; H, 6.40; N, 5.74.

**1,3-Dimethyl-3-(*o*-tolyl)oxindole (30).** Substrate **29** (332 mg, 1.00 mmol), $Pd(OAc)_2$ (11.2 mg, 0.0500 mmol), $PCy_3$ (14.0 mg, 0.0500 mmol), and NaO$^t$Bu (144 mg, 1.500 mmol) were used. Reaction at 50 °C for 12 h gave 250 mg (99%) of **30** as colorless oil after silica gel chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.57 (d, $J$ = 7.8 Hz, 1H), 7.18 (m, 2H), 7.11 (m, 1H), 6.96−6.88 (m, 2H), 6.83 (d, $J$ = 7.6 Hz, 1H), 6.77 (d, $J$ = 7.2 Hz, 1H), 3.24 (s, 3H), 1.69 (s, 3H), 1.53 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 179.64, 142.59, 137.48, 136.45, 134.69, 131.31, 127.42, 127.06, 127.00, 125.63, 122.58, 122.52, 107.67, 51.94, 26.09, 25.41, 18.81. FTIR (neat, NaCl plate): 1716 $cm^{-1}$. MS (EI): 251 (100), 236 (10), 193 (42), 179 (40), 130 (5), 115 (12), 91 (10), 63 (9). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.05; H, 6.74; N, 5.43.

**1,3-Dimethyl-3-(4-isobutylphenyl)oxindole (32).** Substrate **31** (112 mg, 0.300 mmol), $Pd(OAc)_2$ (3.3 mg, 0.015 mmol), $PCy_3$ (4.2 mg, 0.015 mmol), and NaO$^t$Bu (43.2 mg, 0.450 mmol) were used. Reaction at 50 °C for 14 h gave 66 mg (75%) of **32** as colorless oil after silica gel chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.23 (td, $J$ = 7.8, 1.2 Hz, 1H), 7.12 (m, 3H), 7.01 (d, $J$ = 7.2 Hz, 1H), 6.97 (d, $J$ = 8.4 Hz, 2H), 6.82 (d, $J$ = 7.6 Hz, 1H), 3.15 (s, 3H), 2.33 (d, $J$ = 7.2 Hz, 2H), 1.73 (m, 1H), 1.69 (s, 3H), 0.79 (d, $J$ = 6.4 Hz, 3H), 0.78 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 180.08, 143.64, 141.07, 138.43, 135.40, 129.68, 128.43, 126.74, 124.63, 123.14, 108.68, 52.31, 45.37, 30.56, 26.89, 24.24, 22.84, 22.82. FTIR (neat, NaCl plate): 1717 $cm^{-1}$. MS (EI): 293 ($M^+$, 100), 268 (80), 250 (45), 222 (35), 207 (30), 160 (20), 130 (7), 91 (8), 77 (5), 51 (3). Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.62; H, 8.12; N, 4.58.

**3-Cyclohexyl-1,3-dimethyloxindole (34).** Substrate **33** (324 mg, 1.00 mmol), $Pd(OAc)_2$ (11.2 mg, 0.0500 mmol), $PCy_3$ (14.0 mg, 0.0500 mmol), and NaO$^t$Bu (144 mg, 1.500 mmol) were used. Reaction at 50 °C for 14 h gave 156 mg (64%) of **34** as colorless oil after silica gel chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.18 (m, 1H), 7.12 (d, $J$ = 8.8 Hz, 1H), 6.96 (ddd, $J$ = 8.0, 7.6, 0.8 Hz, 1H), 6.74 (d, $J$ = 8.0 Hz, 1H), 3.12 (s, 3H), 1.75−1.65 (m, 3H), 1.52 (m, 2H), 1.40 (m, 1H), 1.27 (s, 3H), 1.18−1.04 (m, 3H), 0.92 (m, 1H), 0.69 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 181.63, 144.16, 134.27, 128.10, 124.06, 122.72, 108.28, 52.29, 46.09, 28.07, 27.68, 27.29, 26.94, 26.81, 26.57, 21.59 ppm. FTIR (neat, NaCl plate): 1715 $cm^{-1}$. MS (EI): 243 (13), 161 (100), 130 (7), 117 (10), 77 (7), 55 (9). Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.75. Found: C, 78.69; H, 8.83; N, 5.47.

**1-Methyl-3-(2-spirotetrahydrofuranyl)oxindole (36).** Substrate **35** (142 mg, 0.500 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $PCy_3$ (7.0 mg, 0.025 mmol), and NaO$^t$Bu (72.0 mg, 0.750 mmol) were used. Reaction at 50 °C for 24 h gave 99.5 mg (98%) of **36** as a colorless oil after silica gel chromatography. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.33 (m, 2H), 7.08 (ddd, $J$ = 7.6, 7.4, 0.8 Hz, 1H), 6.80 (d, $J$ = 7.6 Hz, 1H), 4.32 (m, 1H), 4.26 (m, 1H), 3.17 (s, 3H), 2.47 (m, 1H), 2.37 (m, 1H), 2.25 (m, 1H), 2.14 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 178.53, 144.20, 131.18, 130.21, 124.05, 123.65, 108.86, 83.39, 70.97, 36.55, 27.09, 26.72. FTIR (neat, NaCl plate): 1723 $cm^{-1}$. MS (EI): 203 ($M^+$, 67), 159 (100), 133 (75), 117 (40), 77 (40), 51 (11). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.73; H, 6.57; N, 6.77.

**3-Cyclohexyl-1-methyloxindole (14).** Substrate **42** (265 mg, 1.00 mmol), $Pd(OAc)_2$ (11.2 mg, 0.0500 mmol), $PCy_3$ (14.0 mg, 0.0500 mmol), and NaO$^t$Bu (144 mg, 1.500 mmol) were used. Reaction at 70 °C for 24 h gave 149 mg (65%) of **14** after silica gel chromatography. Recrystallization from hexanes gave a white solid (mp 80−81 °C). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.28 (m, 2H), 7.05 (t, $J$ = 7.68 Hz, 1H), 6.82 (d, $J$ = 8.0 Hz, 1H), 3.35 (d, $J$ = 3.0 Hz, 1H), 3.20 (s, 3H), 2.16 (m, 1H), 1.78−1.66 (m, 4H), 1.48−1.07 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 178.08, 145.45, 128.39, 125.07, 122.72 (2C), 108.42, 52.21, 41.64, 31.05, 29.05, 27.38, 27.00, 26.78, 26.66. FTIR (KBr): 1710 $cm^{-1}$. MS (EI): 229 ($M^+$, 13), 147 (100), 118 (9), 91 (9), 77 (5), 55 (10). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.41; H, 8.25; N, 5.98.

**General Procedure for the Synthesis of Oxindoles from *N*-(2-Bromophenyl)-*N*-methylacetamide and Aryl Chloride Using $PCy_3$ as Ligand.** In the drybox, $Pd(OAc)_2$ (22.4 mg, 0.100 mmol), $PCy_3$ (28.0 mg, 0.100 mmol), and NaO$^t$Bu (288 mg, 3.00 mmol) were combined in a small round-bottom flask. 1,4-Dioxane (3.0 mL) was added, and the flask was sealed with a septum. The resulting mixture was allowed to stir for 1 min, at which time the *N*-(2-bromophenyl)-*N*-methylacetamide **9** (235 mg, 1.03 mmol) and aryl chloride substrate (1.0 mmol) were added. After being removed from the drybox, the flask was placed in an oil bath at 70 °C until the starting material was consumed, as determined by GC and TLC. The reaction was poured into 10 mL of saturated aqueous ammonium chloride and extracted (3 × 20 mL) with $Et_2O$. The combined ether extracts were washed with brine (60 mL), dried over $MgSO_4$, and filtered. The solvent was removed under vacuum, and the resulting crude product was purified by flash chromatography on silica gel. The product was eluted with 20% ethyl acetate in hexanes.

**1-Methyl-3-(*o*-tolyl)oxindole (48).** *o*-Tolyl chloride (127 mg, 1.00 mmol) was used. Reaction at 70 °C for 12 h gave 134 mg (56%) of **48** after silica gel chromatography. Recrystallization from hexanes gave a white solid (mp 131−132 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.24 (m, 1H), 7.17−6.93 (m, 6H), 6.82 (d, $J$ = 7.8 Hz, 1H), 4.76 (br s, 1H), 3.19 (s, 3H), 2.29 (br s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 176.58, 144.77, 137.60, 135.81, 131.40, 129.61, 128.64 (2C), 128.08, 126.74, 124.98, 123.15, 108.48, 50.64, 26.84, 20.17. FTIR (KBr): 1709 $cm^{-1}$. MS (EI): 237 ($M^+$, 100), 208 (38), 194 (37), 179 (30), 165 (28), 152 (11), 118 (10), 91 (11), 51 (4). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.72; H, 6.11; N, 5.78.

**1-Methyl-3-(*p*-tolyl)oxindole (49).** *p*-Tolyl chloride (127 mg, 1.00 mmol) was used. Reaction at 70 °C for 12 h gave 132 mg (55%) of **49** after silica gel chromatography. Recrystallization from hexanes gave a white solid (mp 95−96 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.35 (m, 1H), 7.17 (m, 3H), 7.08 (m, 3H), 6.92 (d, $J$ = 7.8 Hz, 1H), 4.60 (s, 1H), 3.28 (s, 3H), 2.35 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 176.82, 145.12, 137.88, 134.21, 130.21, 129.68, 128.96, 128.90, 125.63, 123.33, 108.75, 52.33, 27.09, 21.76. FTIR (KBr): 1716 $cm^{-1}$. MS (EI): 237 ($M^+$, 100), 208 (56), 194 (48), 165 (15), 151 (10), 118 (10), 91 (8), 51 (2). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.73; H, 6.09; N, 5.86.

**1-Methyl-3-(2-methoxyphenyl)oxindole (50).** 2-Chloroanisole (142 mg, 1.00 mmol) was used. Reaction at 70 °C for 12 h gave 152 mg (60%) of **50** after silica gel chromatography. Recrystallization from hexanes gave a white solid (mp 106−107 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.21−7.16 (m, 2H), 6.99 (m, 2H), 6.90 (m, 1H), 6.85−6.78 (m, 3H), 4.81 (s, 1H), 3.66 (s, 3H), 3.22 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 177.47, 158.15, 144.94, 130.66, 130.46, 129.54, 128.47, 126.63, 124.77, 123.06, 121.61, 112.10, 108.36, 56.45, 48.56, 27.07. FTIR (KBr): 1715 $cm^{-1}$. MS (EI): 253 ($M^+$, 100), 238 (80), 210 (50), 194 (24), 181 (20), 165 (20), 152 (21), 139 (10), 127 (5), 115 (8), 102 (3), 91 (5), 77 (5), 63 (4), 51 (3). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.59; H, 5.75; N, 5.44.

**3-(1,3-Benzodioxol-5-yl)-1-methyloxindole (51).** 5-Chloro-1,3-benzodioxole (127 mg, 1.00 mmol) was used. Reaction at 70 °C for 12 h gave 134 mg (56%) of **51** after silica gel chromatography. Recrystallization from hexanes gave a white solid (mp 131−132 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.34 (m, 1H), 7.17 (d, $J$ = 7.3 Hz, 1H), 7.08 (m, 1H), 6.90 (d, $J$ = 8.0 Hz, 1H), 6.78 (d, $J$ = 8.0 Hz, 1H), 6.72 (dd, $J$ = 6.4, 1.7 Hz, 1H), 6.64 (d, $J$ = 1.7 Hz, 1H), 5.92 (s, 2H), 4.52 (s, 1H), 3.25 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 176.56, 148.55, 147.63, 144.91, 130.73, 129.41, 129.00, 125.51, 123.29, 122.45, 109.22, 109.04, 108.73, 101.65, 52.18, 26.99. FTIR (KBr): 1716 cm$^{-1}$. MS (EI): 267 ($M^+$, 100), 232 (61), 209 (33), 152 (30), 139 (25), 118 (20), 76 (22), 51 (10). Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.67; H, 4.69; N, 5.09.

**Ligand 70.** Ligand **70** was prepared by literature methods using (+)-diaminocyclohexane instead of the racemic diamine. $[\alpha]^{24}_D$ = +29.8° ($c$ = 1.0, $CH_2Cl_2$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.45 (s, 1H), 7.27 (s, 2H), 7.00 (s, 2H), 4.12 (m, 2H), 2.36 (s, 6H), 2.31 (s, 12H), 2.02 (m, 4H), 1.78 (m, 2H), 1.42 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 161.15, 140.61, 136.15, 134.68, 130.33, 130.12, 128.99, 70.87, 27.47, 23.76, 21.11, 18.59, 17.89.

***N,N′*-Diisopinocampheylimidazolinium Tetrafluoroborate (71).** A round-bottom flask was charged with (−)-isopinocamphenylamine (1.796 g, 11.71 mmol) in 10 mL of $CH_2Cl_2$. Aqueous glyoxal (40%, 849 mg, 5.86 mmol) was added at 0 °C. The resulting solution was allowed to warm to room temperature and to stir for 5 h. The reaction was diluted with $Et_2O$, and the organic phase was washed with water, dried over $MgSO_4$, filtered, and dried in vacuo. The crude product (1.92 g, 5.86 mmol) was used in the following reaction without further purification. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.79 (s, 2H), 3.38 (m, 2H), 2.34 (m, 2H), 2.19 (m, 2H), 2.00 (m, 2H), 1.91 (m, 2H), 1.80 (m, 4H), 1.17 (s, 6H), 1.11 (m, 2H), 0.97 (s, 6H), 0.93 (d, $J$ = 7.3 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 159.82, 70.39, 47.80, 43.70, 41.90, 39.20, 36.05, 34.28, 28.36, 23.93, 20.23.

The diimine (1.92 g, 5.86 mmol) was dissolved in dichloromethane in a round-bottom flask, and $NaBH(OAc)_3$ (3.104 g, 14.65 mmol) was added. The resulting mixture was allowed to stir for 24 h at room temperature. The reaction mixture was quenched by adding aqueous saturated $NH_4Cl$, and the product was extracted with $Et_2O$. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The resulting crude product was purified by flash chromatography on silica gel (EtOAc/hexane = 1:1). A colorless oil (1.05 g, 3.16 mmol) was obtained. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.84 (m, 4H), 2.71 (m, 2H), 2.36 (m, 4H), 1.94 (m, 2H), 1.79 (m, 4H), 1.62 (m, 4H), 1.21 (s, 6H), 1.11 (d, $J$ = 7.2 Hz, 6H), 0.98 (s, 6H), 0.94 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 56.88, 48.03, 47.72, 45.20, 41.84, 38.65, 36.93, 33.89, 27.93, 23.48, 21.91.

A 10 mL round-bottom flask charged with triethyl orthoformate (486 mg, 3.16 mmol) ammonium tetrafluoroborate (331 mg, 3.16 mmol) and diamine (1.05 g, 3.16 mmol) was heated at 120 °C in an oil bath for 2 h. The ethanol formed during the reaction was removed in vacuo. The crude product was crystallized from absolute ethanol to give 870 mg (2.02 mmol, 64%) of white needles (mp >330 °C dec). $[\alpha]_D$ = −36.7° ($c$ = 0.52, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CD_2Cl_2$): $\delta$ 8.23 (s, 1H), 4.22 (m, 2H), 3.93 (m, 4H), 2.40 (m, 4H), 2.01 (ddd, $J$ = 7.8, 7.6, 1.6 Hz, 2H), 1.96 (m, 2H), 1.84−1.76 (m, 4H), 1.17 (s, 6H), 1.06 (d, $J$ = 7.2 Hz, 6H), 0.96 (s, 6H), 0.75 (d, $J$ = 9.6 Hz, 2H). $^{13}$C NMR (100 MHz, $CD_2Cl_2$): $\delta$ 157.78, 58.65, 47.84, 44.29, 41.96, 40.84, 39.13, 35.35, 32.62, 28.35, 23.84, 20.56. Anal. Calcd for $C_{23}H_{39}BF_4N_2$: C, 64.19; H, 9.13; N, 6.51. Found: C, 63.90; H, 8.84; N,6.39.

***N,N′*-Dibornylimidazolinium Tetrafluoroborate (72).** The same procedure as in the preparation of **74** was used. The reaction of (+)-bornylamine (500 mg, 3.26 mmol) and glyoxal (40%, 236 mg, 1.63 mmol) gave the corresponding diimine (515 mg, 1.57 mmol). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.95 (m, 2H), 3.42 (m, 2H), 2.18 (m, 2H), 2.03 (m, 2H), 1.79 (m, 2H), 1.73 (m, 2H), 1.37 (m, 2H), 1.34 (m, 2H), 1.28 (m, 2H), 0.95 (d, $J$ = 1.2 Hz, 6H), 0.92 (d, $J$ = 1.6 Hz, 6H), 0.73 (d, $J$ = 2.0 Hz, 6H). $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$ 161.79, 76.05, 51.39, 49.16, 46.07, 37.91, 29.15, 28.77, 20.33, 19.42, 14.18.

The reduction of the diimine (515 mg, 1.57 mmol) with $NaBH(OAc)_3$ (827 mg, 3.92 mmol) gave the corresponding diamine (308 mg, 0.928 mmol). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.71 (m, 4H), 2.57 (m, 2H), 2.08 (m, 2H), 1.71 (m, 2H), 1.61 (m, 2H), 1.53 (m, 2H), 1.18 (m, 4H), 1.10 (m, 2H), 0.80 (s, 6H), 0.78 (s, 12H), 0.73 (dd, $J$ = 12.4, 4.4 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 63.34, 49.10 (2C), 48.64, 45.41, 38.61, 28.84, 27.78, 20.27, 19.08, 14.72.

Reaction of the diamine (308 mg, 0.928 mmol) with triethyl orthoformate (137 mg, 0.928 mmol) and ammonium tetrafluoroborate (97.3 mg, 0.928 mmol) gave **72** (366 mg, 0.853 mmol, 92%). Recrystallization from ethanol gave a white solid (mp 280−282 °C). $[\alpha]^{24}_D$ = +14.0° ($c$ = 0.73, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.84 (s, 1H), 4.06 (m, 2H), 3.94 (m, 2H), 3.90 (m, 2H), 2.27 (m, 2H), 1.76 (m, 2H), 1.71 (m, 2H), 1.43 (m, 2H), 1.35−1.17 (m, 6H), 0.89 (s, 6H), 0.87 (s, 6H), 0.83 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 157.77, 65.12, 51.09, 50.55, 49.40, 44.72, 32.78, 28.44, 28.20, 20.02, 18.81, 14.60. Anal. Calcd for $C_{23}H_{39}BF_4N_2$: C, 64.19; H, 19.13; N, 6.51. Found: C, 63.90; H, 9.17; N, 6.23.

**Asymmetric Synthesis of Oxindoles.** The same method was followed as was described in the general synthesis of racemic oxindoles, except $Pd(dba)_2$ and optically active ligands were used in monoglyme solvent. The enantiomeric excess was determined by $^1$H NMR spectroscopy using the chiral shift reagent $Eu(hfc)_3$ and by HPLC analysis with a chiral column (Chiral Daicel OD-H; 25 cm × 0.46 cm; hexane/*i*-PrOH = 98:2, UV−vis 254 nm).

**1-Benzyl-3-(1-naphthyl)-3-methyloxindole (24).** A mixture of **24** (10.8 mg, 0.0300 mmol) and $Eu(hfc)_3$ (7.1 mg, 0.0059 mmol) in $CDCl_3$ (0.8 mL) showed two separate peaks at 5.56 ppm ((−)-**24**) and 5.48 ppm ((+)-**24**) in the $^1$H NMR spectrum for the *N*-methylene group of the two enantiomers. HPLC analysis gave two separate peaks (flow rate: 2.0 mL/min, $t_R$ = 10.42 min ((+)-**24**), 23.04 min ((−)-**24**)). Reactions employing ligand **71** gave 67% ee (HPLC), $[\alpha]^{24}_D$ = +30.8° ($c$ = 1.00, $CH_2Cl_2$), and reactions employing ligand **72** gave 76% ee (HPLC), $[\alpha]^{24}_D$ = −32.2° ($c$ = 1.55, $CH_2Cl_2$).

**1,3-Dimethyl-3-(1-naphthyl)oxindole (26).** A mixture of **26** (7.7 mg, 0.027 mmol) and $Eu(hfc)_3$(3.0 mg, 0.0025 mmol) in $CDCl_3$ (0.8 mL) showed two separate peaks at 3.85 ppm-((+)-**26**) and 3.74 ppm((−)-**26**) in the $^1$H NMR spectrum for the *N*-methyl group of the two enantiomers. HPLC analysis gave two separate peaks (flow rate: 1.5 mL/min, $t_R$ = 15.32 min ((−)-**26**), 39.67 min ((+)-**26**)). Reactions employing ligand **71** gave 67% ee (HPLC), $[\alpha]^{24}_D$ = −3.5° ($c$ = 0.62, $CH_2Cl_2$), and reactions employing ligand **72** gave 69% ee (HPLC), $[\alpha]^{24}_D$ = +7.7° ($c$ = 1.30, $CH_2Cl_2$).

**1,3-Dimethyl-3-phenyloxindole (28).** A mixture of **28** (10.5 mg, 0.0443 mmol) and $Eu(hfc)_3$ (4.4 mg, 0.0037 mmol) in $CDCl_3$ (0.8 mL) showed two separate peaks at 3.76 ppm ((−)-**28**) and 3.67 ppm ((+)-**28**) in the $^1$H NMR spectrum for the *N*-methyl group of the two enantiomers. HPLC analysis gave two separate peaks (flow rate: 2.0 mL/min, $t_R$ = 5.48 min ((−)-**28**), 6.55 min ((+)-**28**)). Reactions employing ligand **71** gave 34% ee (HPLC), $[\alpha]^{24}_D$ = −27.7° ($c$ = 2.97, $CH_2Cl_2$), and reactions employing ligand **72** gave 57% ee (HPLC), $[\alpha]^{24}_D$ = +41.1° ($c$ = 0.84, $CH_2Cl_2$).

**1,3-Dimethyl-3-(*o*-tolyl)oxindole(30).** A mixture of **30** (25.1 mg, 0.100 mmol) and $Eu(hfc)_3$ (11.8 mg, 0.0099 mmol) in $CDCl_3$ (0.8 mL) showed two separate peaks at 3.83 ppm ((−)-**30**) and 3.78 ppm ((+)-**30**) in the $^1$H NMR spectrum for the *N*-methyl group of the two enantiomers. HPLC analysis gave two separate peaks (flow rate: 2.0 mL/min, $t_R$ = 6.44 min ((+)-**30**), 9.53 min ((−)-**30**)). Reactions employing ligand **75** gave 33% ee (HPLC), $[\alpha]^{24}_D$ = +18.7° ($c$ = 1.23, $CH_2Cl_2$), and reactions employing ligand **76** gave 42% ee (HPLC), $[\alpha]^{24}_D$ = −23.9° ($c$ = 1.45, $CH_2Cl_2$).

**1,3-Dimethyl-3-(4-isobutylphenyl)oxindole (32).** A mixture of **32** (6.7 mg, 0.0228 mmol) and $Eu(hfc)_3$ (2.6 mg, 0.0022 mmol) in $CDCl_3$ (0.8 mL) showed two separate peaks at 3.80 ppm ((−)-**32**) and 3.74 ppm ((+)-**32**) in the $^1$H NMR spectrum for the *N*-methyl group of the two enantiomers. HPLC analysis

gave two separate peaks (flow rate: 1.0 mL/min, $t_R = 7.96$ min ((−)-**32**), 8.77 min ((+)-**32**)). Reactions employing ligand **71** gave 40% ee (HPLC), $[\alpha]^{24}_D = -27.9°$ ($c = 2.97$, $CH_2Cl_2$), and reactions employing ligand **72** gave 50% ee (HPLC), $[\alpha]^{24}_D = +39.9°$ ($c = 1.09$, $CH_2Cl_2$).

**Synthesis of Palladium Complex 73a.** In the drybox, Pd(dba)$_2$ (575 mg, 1.00 mmol), $PCy_3$ (280 mg, 1.00 mmol) and **1** (358 mg, 1.40 mmol) were stirred in benzene for 20 h at room temperature. A white solid precipitated from solution. The solid was collected by filtration and was washed with $Et_2O$ and then dried in vacuo. Recrystallization from $CH_2Cl_2/Et_2O$ (1/1) gave a white solid 385 mg (0.600 mmol, 60%). $^1$H NMR (400 MHz, $CD_2Cl_2$): $\delta$ 7.13 (m, 1H), 6.84 (m, 2H), 6.69 (m, 1H), 3.43 (s, 3H), 2.91 (sept, $J = 6.6$ Hz, 1H), 2.05 (m, 3H), 1.44−1.35 (m, 18H), 1.16 (br s, 6H), 1.06 (m, 6H), 0.69 (br s, 6H). $^{13}$C NMR (100 MHz, $CD_2Cl_2$): $\delta$ 181.71 (d, $J_{c-p} = 2.7$ Hz), 145.52 (d, $J_{c-p} = 3.7$ Hz), 141.76, 137.64 (d, $J_{c-p} = 5.3$ Hz), 127.69 (d, $J_{c-p} = 3.7$ Hz), 125.35, 117.74, 36.32, 36.10 (d, $J_{c-p} = 24.4$ Hz), 32.68, 30.86, 28.27 (d, $J_{c-p} = 11.2$ Hz), 27.20, 19.74. $^{31}$P NMR ($CD_2Cl_2$, 162 MHz): $\delta$ 51.89 (s). FTIR (KBr pellet): 1645 cm$^{-1}$. Anal. Calcd for $C_{29}H_{47}BrNOPPd$: C, 54.17; H, 7.37; N, 2.17. Found: C, 53.87; H, 7.08; N, 1.99.

**Synthesis of Palladium Complex 73b.** In the drybox, Pd(PCy$_3$)$_2$ (205 mg, 0.307 mmol) and **1** (105 mg, 0.410 mmol) were stirred in benzene for 48 h at room temperature. A white solid precipitated from solution. The solid collected by filtration, and was washed with $Et_2O$ and then dried in vacuo. Recrystallization from $CH_2Cl_2/Et_2O$ (1/1) gave a white solid 170 mg (0.184 mmol, 60%). $^1$H NMR (400 MHz, $CD_2Cl_2$): $\delta$ 7.58 (br s, 1H), 6.67 (br s, 2H), 6.59 (br s, 1H), 3.76 (br s, 3H), 2.72−2.47 (br s, 1H), 2.03 (br s, 4H), 1.74 (br s, 12H), 1.48−1.36 (m, 30H), 0.94 (br s, 26H). $^{13}$C NMR (100 MHz, $CD_2Cl_2$): $\delta$ 179.11, 148.13, 142.58, 129.07, 127.57, 124.25, 123.35, 39.65, 35.54, 32.16, 30.98, 28.38, 27.18, 22.40, 19.45. $^{31}$P NMR ($CD_2Cl_2$, 162 MHz): $\delta$ 21.27 (s). FTIR (KBr pellet): 1651 cm$^{-1}$. Anal. Calcd for $C_{47}H_{80}BrNOP_2Pd$: C, 54.17; H, 7.37; N, 2.17. Found: C, 53.87; H, 7.08; N, 1.99.

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