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Stereoselective Synthesis of Unsymmetrical β,β-Diarylacrylates by a Heck−Matsuda Reaction: Versatile Building Blocks for Asymmetric Synthesis of β,β-Diphenylpropanoates, 3-Aryl-indole, and 4-Aryl-3,4-dihydro-quinolin-2-one and Formal Synthesis of (−)-Indatraline

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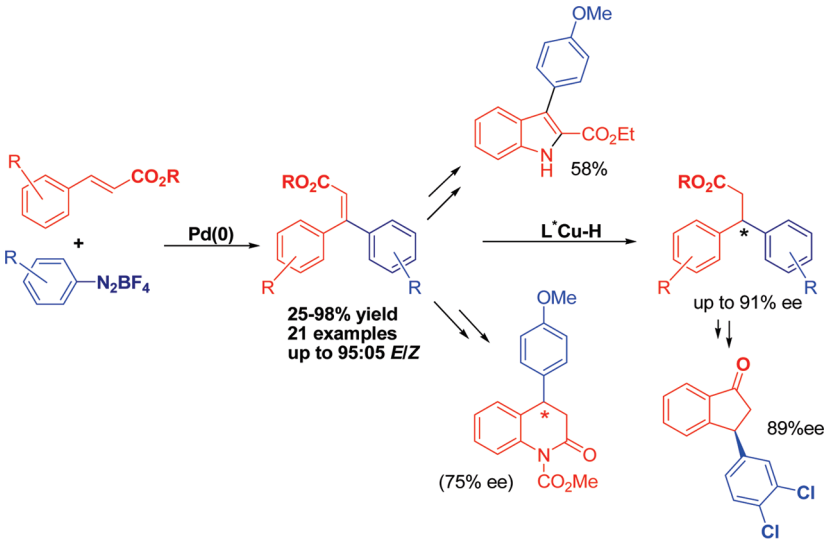

β,β-Disubstituted α,β-unsaturated esters may serve as valuable derivatives for the preparation of other highly functionalized systems found in many natural products and marketed drugs. The stereoselective synthesis of unsymmetrical β,β-diarylacrylate compounds possessing two similar aromatic groups remains a substantial challenge. A simple and convenient stereoselective protocol for the preparation of β,β-disubstituted acrylates via a Heck−Matsuda reaction is reported. Good to high yields were accomplished by a "ligand-free" Pd-catalyzed arylation reaction of cinnamate esters with arenediazonium tetrafluoroborates. Both electron-deficient and electron-rich arenediazonium salts could be employed as arylating reagents, and cinnamate esters were generally more reactive when substituted with an electron-donating group. The overall methodology is highly stereoselective, and this attribute was taken advantage of in the asymmetric Cu-catalyzed 1,4 reduction reaction to provide β,β-diarylpropanoates in high enantioselectivities. The synthesis of a 3-aryl indole and a chiral 4-aryl-2-quinolone from β,β-diarylacrylates was achieved by cyclization in the presence of a diphosphine ligated CuH catalyst. A convenient route for the asymmetric formal synthesis of the psychoactive compound (−)-Indatraline is also presented.

Introduction

The palladium-catalyzed coupling of arenediazonium salts to olefins (often referred to as a Heck−Matsuda reaction (HM)) has attracted considerable interest as a convenient alternative to traditional Heck protocols, and has been increasingly applied in organic synthesis.[1] This methodology is particularly interesting in the construction of complex arylated compounds. Among those, the unsaturated diaryl substituted carbon centers are

(1) (a) Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1977**, 159. For a review, see: (b) Roglans, A.; Pla-Quintana, A.; Moreno-Manas *Chem. Rev.* **2006**, *106*, 4622.

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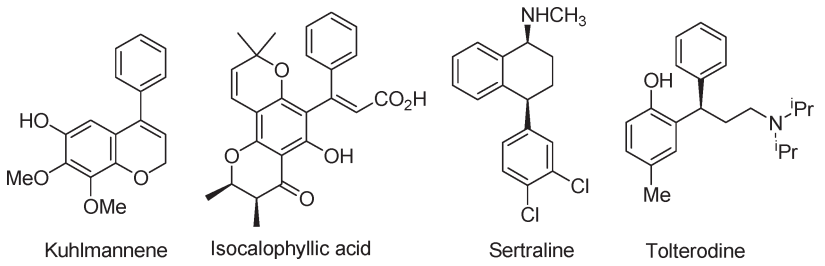


FIGURE 1. Unsaturated diaryl substituted carbon centers in natural products Kuhlmannene and Isocalophyllic Acid.

relevant frameworks because they are present in natural products like Kuhlmannene[2a] and Isocalophyllic acid[2b] (Figure 1), and they can also be precursors for the synthesis of marketed drugs such as Sertraline[3a] and Tolterodine.[3b]

β,β-Disubstituted α,β-unsaturated esters may serve as valuable derivatives for the preparation of highly functionalized olefin systems such as α,β -enals and -enones, and α,β-unsaturated acrylamides. Although symmetrical β,β-diarylacrylates can be accessed by Wittig olefination of functionalized benzophenones with a stabilized phosphorus ylide, unsymmetrical substituted benzophenones typically afford the corresponding α,β-unsaturated esters in poor stereoselectivities.[4] In comparison, the application of CuOAc as catalyst in the conjugate addition of arylboronic acids to alkynoates was shown to be a highly effective methodology for the stereoselective synthesis of trisubstituted cinnamates.[5] In this study, Yamamoto, Kirai and Harada demonstrated with 5 examples that using 1−3 mol % CuOAc, electronically rich, poor and neutral phenylboronic acids could be reacted with ethyl phenylpropiolate to provide the corresponding β,β-diarylacrylates in high yields as single stereoisomers.

Heck arylations of β-substituted α,β-unsaturated carbonyl compounds have been the subject of several investigations, with the achievement of a stereoselective synthesis being the main challenge.[6] Several studies have been reported for the Pd-catalyzed arylation of cinnamic esters with aryl halides but often lacking examples for unsymmetrical β,β-diarylacrylates functionalized on both aromatic rings.[7] Calo et al. demonstrated that Pd nanoparticles could efficiently catalyze the stereospecific coupling of cinnamates with aryl halides at 130 °C using tetrabutylammonium acetate as base, dissolved in tetrabutylammonium bromide.[8] The substrate scope was explored and among the eleven examples presented, five were derived from a substituted cinnamate ester but only in two cases the product was functionalized on both aromatic rings.

Unsymmetrical β,β-diaryl cinnamic acids and esters have been shown to be useful intermediates for the synthesis of medicinal products as illustrated in two different reports where the target compounds were accessed by a Heck arylation reaction and thus exemplifying the utility of this strategy in the construction of interesting molecules.[9] However, when traditional Heck protocols are employed for the synthesis of β,β-diarylacrylates, they are often disadvantaged by the necessity for long reaction times, an inert atmosphere, elevated temperatures and often lacking high control in the stereochemistry of the process. On the other hand, arenediazonium salts can be employed in the absence of phosphines as ligand and thus negating the requirement for aerobic conditions, which makes the reaction more practical and easier to handle.[10] Additionally, the reaction can be performed with or without a base and it is often faster than traditional Heck protocols.[11] Recently, we reported the use of arenediazonium salts as arylating agents for methyl cinnamate in a highly effective and stereoselective Pd-catalyzed Heck−Matsuda reaction.[3a] However, a new, mild, straightforward and highly selective method that can provide unsymmetrical β,β-diarylacrylates is still desired. We reasoned that applying the Heck-Matsuda protocol toward the synthesis of unsymmetrical β,β-diarylacrylates would provide convenient access to these compounds and expand the available methods for their synthesis.

Herein, we describe a method of synthesizing unsymmetrical β,β-diarylacrylates in high stereoselectivity from cinnamate ester derivatives via a Heck−Matsuda procedure. The utility of this protocol is further exemplified by the application toward the synthesis of optically enriched β,β-diphenylpropanoates, a 4-aryl-3,4-dihydro-quinolin-2-one and the formal asymmetric synthesis of Indatraline.

Results and Discussion

The present technique for producing β,β-diarylacrylates relies on the efficient synthesis of cinnamate esters in stereoisomerically pure form. All of the cinnamate derivatives discussed in this paper were easily prepared by either a Wittig−Horner reaction (using commercially available benzaldehydes) or by a Heck Matsuda reaction with methylacrylate (Figure 2). These substrates were purified by recrystallization or chromatography, and were synthesized according to literature procedures, which accentuates the usefulness of this method (see Supporting Information for details).

(2) (a) Ollis; et al. *Chem. Commun.* **1968**, 1392. (b) Alarcon, A. B.; Cuesta-Rubio, O.; Perez, J. C.; Piccinelli, A. L.; Rastrelli, L. *J. Nat. Prod.* **2008**, *71* (7), 1283.

(3) (a) Pastre, J. C.; Correia, C. R. D. *Adv. Synth. Catal.* **2009**, *351*, 1217. (b) Gallagher, B. D.; Taft, R.; Lipshutz, B. H. *Org. Lett.* **2009**, *11* (23), 5374.

(4) For examples see: (a) Malamas, M. S.; Palka, C. L. *J. Heterocycl. Chem.* **1996**, *33* (2), 475. (b) Almansa, C. A.; et al. *J. Med. Chem.* **1996**, *39* (11), 2197. (c) Yu, K.-L.; et al. *J. Med. Chem.* **1996**, *39* (12), 2411.

(5) Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Commun.* **2008**, 2010.

(6) For reports on Heck coupling reactions of aryl halides to α,β-unsaturated carbonyl compounds, see: (a) Cacchi, S. *Palmieri Synthesis* **1984**, *7*, 575. (b) Baek, G. H.; et al. *Bull. Korean Chem. Soc.* **1999**, *20* (2), 232. (c) Bernini, R.; Cacchi, S.; Salve, I. D.; Fabrizi, G. *Synlett* **2006**, *18*, 2947.

(7) (a) Moreno-Manas, M.; Perez, M.; Pleixats, R. *Tetrahedron Lett.* **1996**, *37*, 7449. (b) Gurtler, C.; Buchwald, S. L. *Chem.—Eur. J.* **1999**, *5*, 3107. (c) Botella, L.; Carmen Nájera, C. *J. Org. Chem.* **2005**, *70* (11), 4360.

(8) Calo, V.; Nacci, A.; Monopoli, A.; Laera, S.; Cioffi, N. *J. Org. Chem.* **2003**, *68*, 2929.

(9) (a) Ikemoto, T.; et al. *Tetrahedron Lett.* **2004**, *45*, 7757. (b) Song, F. et al *J. Med. Chem.* **2007**, *50*, 2807.

(10) Sengupta, S.; Bhattacharyya, S. *Tetrahedron Lett.* **2001**, *42*, 2035.

(11) (a) Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31. (b) Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1977**, 159.

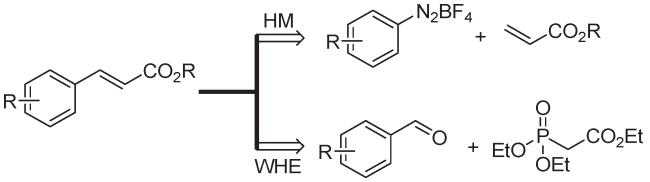
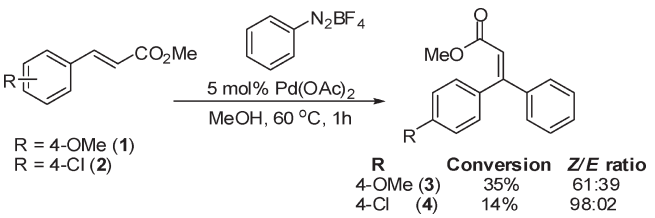


FIGURE 2. Preparation of cinnamate ester substrates.

SCHEME 1. Monitoring of Competitive HM-Reaction by GC-MS



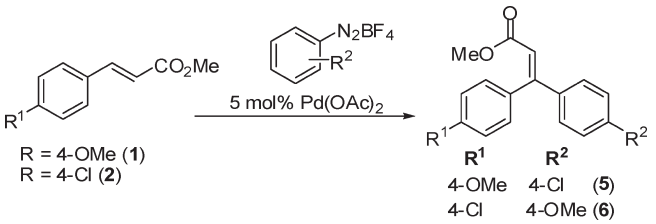
Using our previously reported procedure for the arylation of methyl cinnamate, $Pd(OAc)_2$ and methanol as solvent were employed for the investigation of the 4-methoxy and 4-chloro substituted cinnamate esters (**1** and **2** respectively). To understand how the electronic properties affect the reaction rate and stereoselectivity of the process, a competitive experiment was carried out. Using GC-MS to monitor the reaction outcome, cinnamate esters **1** and **2** were both reacted in the same flask with benzene diazonium tetrafluoroborate in equimolar ratios (Scheme 1).

Although benzene diazonium tetrafluoroborate was not particularly reactive in this initial investigation, this early result indicated that electronically rich olefins were more reactive than electronically poor cinnamate esters but they had a tendency to be less stereoselective. Mindful of the fact that the electronic properties of the olefin influence both its reactivity and stereoselectivity in the coupling reaction, substrates **1** and **2** were utilized for optimization studies (Table 1).

We were pleased to find that the catalyst loading could be reduced to 5 mol % whereas 10 mol % of $Pd(OAc)_2$ was required in our previous study involving methyl cinnamate.[3a] In the arylation of **1** with the 4-chloro substituted arenediazonium salt (1.5 equiv), both trifluoroethanol and acetonitrile (under an atmosphere of CO to reduce Pd^{II} to Pd^0) as solvent failed to afford the expected Heck adduct **5** and the olefin remained unreacted (entries 1 and 2). The reaction proceeded well in methanol, but as previously mentioned, the stereoselectivities were modest and only marginally improved by conducting the reaction at lower temperature (entries 3 and 4). Several bases were screened and all found to have dramatically improved the stereoselectivity of the reaction (entries 5−8). Although the stereoselectivity for the Heck adduct was high when using ^{t}BuNOAc as base, the yield was disappointingly poor. Electron deficient arenediazonium salts are susceptible to nucleophilic attack at the electrophilic nitrogen of the diazonium group and can react competitively with the acetate anion, thus eliminating the arylating reagent from the reaction. Barium carbonate was slightly better (entry 6), but in this case, a sterically hindered pyridine DTBMP (2,6-ditertbutyl-4-methyl-pyridine) gave satisfactory results in terms of *E*/*Z* ratio although this was also accompanied by a significant decrease in product yield (entries 7 and 8).

In comparison, **2** could be coupled to the 4-methoxy arenediazonium salt to provide **6** in high stereoselectivity without the assistance of a base in the reaction medium (entry 9). The catalytic performance was particularly sluggish when performed in methanol solvent (entries 9 and 10) but was improved when using a binary solvent mixture of methanol and acetonitrile in a 1:1 ratio (entry 11). We attribute the beneficial effect of acetonitrile to its ability in assisting the stabilization of the cationic intermediate (formed upon oxidative addition), and therefore, inhibiting the formation of palladium black and consequently permitting higher catalytic turnovers. The presence of sodium acetate was found to have positive impact on stereoselectivity and did not result in any

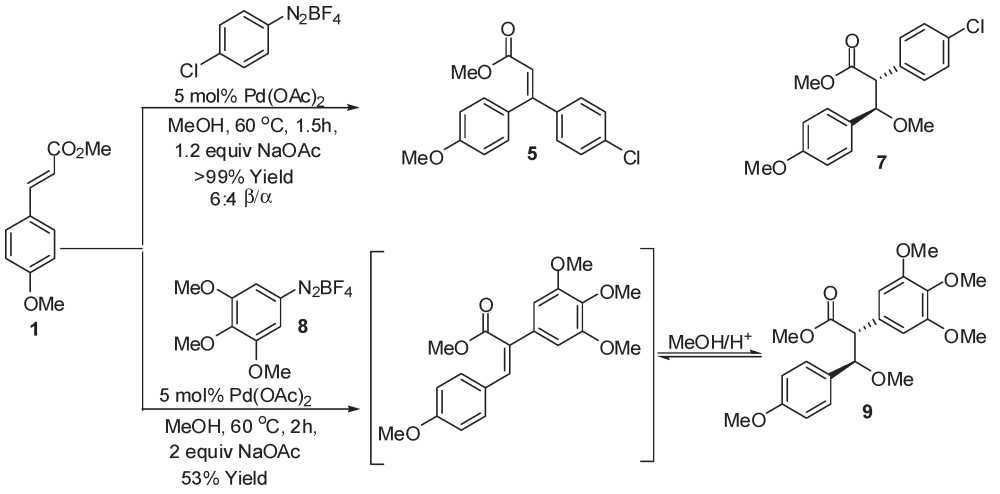
TABLE 1. Reaction Conditions in the Pd-Catalyzed Reaction of Cinnamate Esters with Arenediazonium Salts[a]



entry	R^1	R^2	solvent	T/°C	t/h	base	yields/ %[b]	Z/E ratio[c]
1	4OMe	4Cl	F_3CCH_2OH	80	2	−	NR	NR
2	4OMe	4Cl	MeCN/CO	80	8	−	NR	NR
3	4OMe	4Cl	MeOH	60	1	−	93	42/58
4	4OMe	4Cl	MeOH	25	14	−	78	32/68
5	4OMe	4Cl	MeOH	60	1	^{t}BuN^{+-}OAc	18	01/99
6	4OMe	4Cl	MeOH/MeCN 1:1	80	1	$BaCO_3$	40	01/99
7	4OMe	4Cl	MeOH	60	1	DTBMP	37	08/92
8	4OMe	4Cl	MeOH	25	14	DTBMP	29	03/97
9	4Cl	4OMe	MeOH	60	14	−	39	97/03
10	4Cl	4OMe	MeOH	60	1	−	20	99/01
11	4Cl	4OMe	MeOH/MeCN 1:1	80	14	−	98	72/28
12	4Cl	4OMe	MeOH/MeCN 1:1	25	14	NaOAc	77	97/03

[a]Typical reaction conditions: cinnamate ester (0.50 mmol), arenediazonium salt (1.5 equiv), $Pd(OAc)_2$ (5 mol %), base (1.2 equiv), solvent (3 mL). [b]Isolated yields and NR = No Reaction. [c]Determined by ^{1}H NMR integration.

SCHEME 2. Pd-Catalyzed α-Arylation of Cinnamate Ester with Arenediazonium Salts



significant deterioration of yield (entry 12). Concerning the improvement in stereoselectivity when base was utilized, we have previously rationalized this observation and attributed this result to the scavenging of PdH.[3a] Although methanol is capable of acting as a weak base to reconstitute Pd^0, it is not effective in preventing the reinserting of PdH which is responsible for isomerization of the Heck adducts.

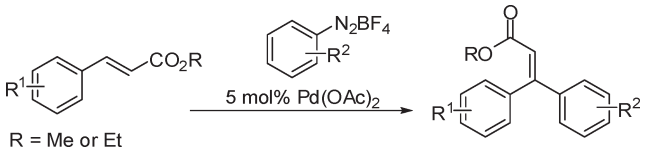
Although sodium acetate was found to be an effective base for the arylation of **2**, surprisingly, the coupling of 4-chloro arenediazonium tetrafluoroborate to **1** afforded an inseparable mixture of the expected *β*-arylated adduct **5** and another unexpected byproduct in a ratio of 6:4. Upon exploration of the reaction scope, we isolated exclusively α-arylated Heck adduct **9** from the reaction of **1** with arenediazonium salt **8** (Scheme 2), and by inference, we concluded that the contaminant coeluting with **5** was **7**.

Compound **9** was isolated in 53% yield and appears to be formed by a reversible *oxa*-Michael addition of methanol to the α-arylated Heck adduct and thus furnishing **9** as a single diastereoisomer albeit in modest yield. In the case of **9**, a doublet resonance in the ^{1}H NMR at 4.55 ppm with a coupling constant of 10.5 Hz was observed and used as a reference to identify **7** and future occurrences for the formation of the α-arylated adduct. An α-arylated Heck-adduct was only observed when the cinnamate ester bearing an electronically donating methoxy substituent was coupled with arenediazonium salts in the presence of sodium acetate. The absence of sodium acetate or use of other bases such as $BaCO_3$ and DTBMP did not have a similar effect. This preliminary result is of interest and is currently under investigation in our laboratory, but results disclosed from here on will focus on the *β*-arylation of cinnamate ester derivatives.

With an understanding of the different factors affecting the arylation of electron rich and poor cinnamate esters, an investigation of the reaction scope was initiated. The results are summarized in Table 2.

The symmetrical *β*,*β*-diarylacrylate **10** was synthesized uneventfully in high yield using an operationally simple procedure in comparison to traditional Heck protocols (entry 1). Given the fact that the synthesis of unsymmetrical *β*,*β*-diarylacrylates with high stereoselectivities is considerably more challenging, our attention was primarily focused on these targets. Compared to the *para*-methoxy substituted arenediazonium salt, coupling of the *ortho*-methoxy equivalent was less reactive although good stereoselectivities were still achievable in this case (entry 2). In contrast to the synthesis of **11**, the coupling of the 3,4-dimethoxy arenediazonium salt proceeded more smoothly suggesting that the electron withdrawing nature of the *meta*-methoxy group (inductive effect) has less of an impact on the reaction outcome than the steric interference provided by the *ortho* methoxy substituent (entries 2 and 3). We envisioned that switching the functional groups around on the reactants would conveniently provide access to the opposite stereoisomers. Indeed, the present method enabled the stereoselective preparation of the opposite stereoisomer of **12** by simply coupling 3,4-dimethoxy cinnamate ester with the appropriate arylating reagent. Unfortunately, the synthesis of **13** in the presence of sodium acetate was hampered by the formation of the aforementioned α-arylated product as a minor impurity (~5%, see Supporting Information), which we were unable to remove by column chromatography. Alternatively when the reaction was carried out in the absence of sodium acetate, it afforded cleanly one regioisomer although the stereoselectivity was very poor (entry 4). Interestingly, a sterically more demanding cinnamate ester was equally as reactive as other electron rich substrates and once again highlighting the stronger influence that *ortho* substituted arenediazonium salts have on product yield (entry 5). Finally, regarding electron rich cinnamate esters, coupling could also be accomplished with electronically poor arylating agents such as the *para*-nitro arenediazonium salt which furnished **15** in excellent yield (entry 6). Turning our attention to the arylation of electronically poor cinnamate esters, we began by attempting the synthesis of **16** (entry 7). Gratifyingly, **16** was prepared in high yield and stereoselectivity comparable with the related chloro Heck-adduct **6** (Table 1, entry 12). Chloro substituted compounds **17**, **18** and **19** were all synthesized in high stereoselectivities, albeit in modest yield for **17** (entries 8−10). Furthermore, the *meta*-chloro Heck adduct **18** was obtained in lower yield than **6**. The final example between an electron rich arenediazonium salt and an electronically poor olefin involves the 2-fluoro substituted cinnamate ester (entry 11). Apparently, the electron withdrawing effect of fluorine in close proximity the double bond resulted in only modest yield of **20** but without negatively

TABLE 2. Pd-Catalyzed Arylation of *trans*-Cinnamates with Arenediazonium Salts[a]



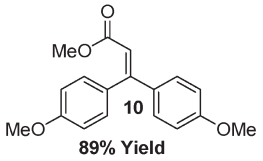
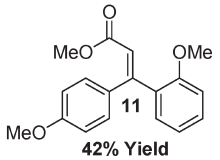
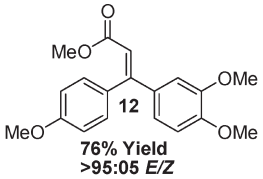
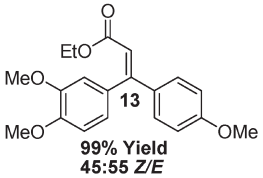
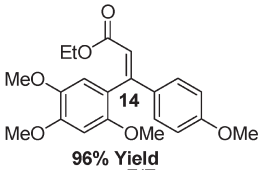
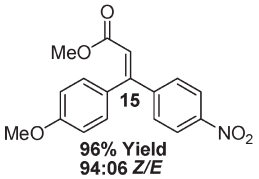
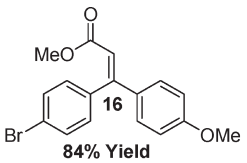
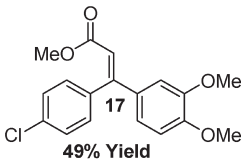
Entry	R^1	R^2	T/ °C	t/ h	Product[b,c]
1[d]	4-OMe	4-OMe	60	1	 **89% Yield**
2[e]	4-OMe	2-OMe	70	1	 **42% Yield 80:20 *E/Z***
3[e]	4-OMe	3,4-OMe	60	2	 **76% Yield >95:05 *E/Z***
4[f,j]	3,4-OMe	4-OMe	70	2	 **99% Yield 45:55 *Z/E***
5[e,g]	2,4,5-OMe	4-OMe	70	2	 **96% Yield 90:10 *Z/E***
6[d]	4-OMe	4-NO_2	25	16	 **96% Yield 94:06 *Z/E***
7	4-Br	4-OMe	60	1	 **84% Yield >95:05 *Z/E***
8	4-Cl	3,4-OMe	25	16	 **49% Yield >95:05 *E/Z***

TABLE 2. Continued

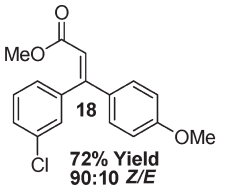
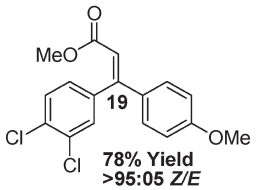
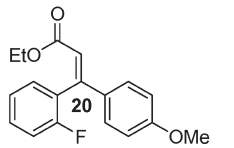
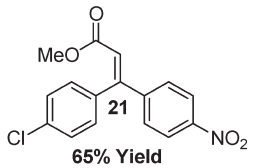
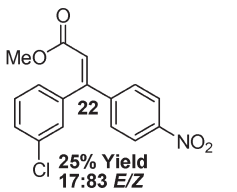
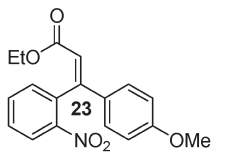
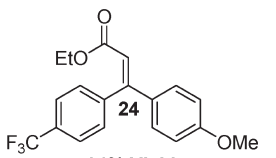
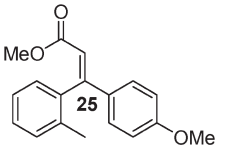
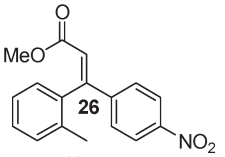
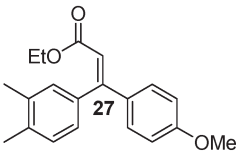
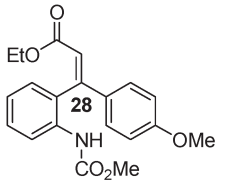
Entry	R^1	R^2	T/ °C	t/ h	Product[b,c]
9	3-Cl	4-OMe	70	2	 **18** **72% Yield** **90:10 *Z/E***
10[i]	3,4-Cl	4-OMe	50	16	 **19** **78% Yield** **>95:05 *Z/E***
11[f]	2-F	4-OMe	65	1	 **20** **48% Yield** **>95:05 *Z/E***
12[d]	4-Cl	4-NO_2	25	16	 **21** **65% Yield** **91:09 *Z/E***
13[d]	3-Cl	4-NO_2	60	2	 **22** **25% Yield** **17:83 *E/Z***
14[g]	2-NO_2	4-OMe	70	16	 **23** **73% Yield** **>95:05 *Z/E***
15[f]	4-CF_3	4-OMe	60	1.5	 **24** **91% Yield** **>95:05 *E/Z***
16	2-Me	4-OMe	70	2	 **25** **73% Yield** **>95:05 *Z/E***

TABLE 2. Continued

Entry	R^1	R^2	T/ °C	t/ h	Product[b,c]
17[j]	2-Me	4-NO_2	70	16	 54% Yield >95:05 *Z/E*
18[f]	3,4-Me	4-OMe	60	1	 91% Yield >95:05 *Z/E*
19[e,g]	2-$NHCO_2Me$	4-OMe	60	14	 87% Yield >95:05 *Z/E*

[a]Typical reaction conditions: cinnamate ester (0.50 mmol), arenediazonium salt (1.5 equiv), $Pd(OAc)_2$ (5 mol %), NaOAc (1.2 equiv), 1:1 MeOH/MeCN (3 mL). [b]Corresponds to isolated yields after purification by column chromatography. [c]Stereoselectivities were determined by ^1H NMR integration. [d]Reaction performed in MeOH and in the absence of a base. [e]2,6-Ditert-butyl-4-methylpyridine was used as base (1.2 equiv). [f]MeCN and EtOH (1:1) were used as solvent. [g]BnCN and EtOH (1:1) were used as solvent. [h]MeOH used as solvent. [i]BnCN and MeOH (1:1) were used as solvent. [j]Reaction performed in the absence of base.

impacting the stereoselectivity. Given the fact that electron deficient cinnamate esters were more resistant to arylation and that electronically poor diazonium salts are less able to stabilize the cationic intermediate (generated upon oxidative addition with Pd^0), this combination of reactants unsurprisingly presented a greater challenge to us. For example, products **21** and **22** were obtained in moderate to low yields (entries 12 and 13) and catalytic performance was particularly sluggish, requiring 16 h in the case of **21**. Unfortunately, the attempted coupling of 4-chloroarenediazonium tetrafluoroborate with **2** failed to provide any Heck adducts and instead, starting material **2** was recovered by column chromatography. Highly electron deficient olefins were only reactive with electron rich arenediazonium salts, as can be seen in the case of *ortho*-nitro and the *para*-trifluoromethane substituted cinnamate esters (entries 14 and 15). In these two reactions, the corresponding arylated products **23** and **24** were isolated in 73 and 91% yield respectively. High stereoselectivities were also realized and in the case of product **23**, a combination of benzonitrile with ethanol was necessary for the attainment of a synthetically useful yield. The evaluation of the substrate scope was completed by the arylation of the methyl substituted cinnamates. In agreement with our previous results,[3a] the success of the arylation was dependent on the arenediazonium salt and the electron rich reagents were once again more reactive than their electronically poor counterparts (entries 16 and 17). We were unsurprised to find that compound **26** could be obtained in high stereoselectivity without the assistance of base. This remarkable dependence on the electronic nature of the arenediazoinium salt was also observed in the arylation of methyl cinnamate.[3a] The observation is also reminiscent of that found in the Heck reaction of aryl iodides with β-arylacrylamides.[6c] Last, but not least, the 3,4-dimethyl substituted cinnamate ester was examined and found to be highly reactive providing product **27** in high yield and stereoselectivity (entry 18). The utility of this methodology is exemplified by the fact that the introduction of an electron-rich aryl group is considerably less efficient when employing traditional Heck protocols,[3a] and in this study, the majority of β,β-diarylacrylates presented bear this motif.

The generally accepted mechanism of the Heck reaction dictates that the stereochemical outcome for the arylation of disubstituted alkenes giving trisubstituted alkenes should proceed in a stereospecific manner and therefore be predictable. However, to alleviate any doubt and to confirm the stereochemistry of those products isolated with exclusive formation of one stereoisomer, NOE experiments were carried out (Figure 3).

Three representative examples are shown in the figure below and all exhibited a nuclear Overhauser enhancement (NOE) of the aromatic resonance when the only olefinic hydrogen present was irradiated, that being the only resonance so affected. Low stereoselectivities have been attributed to a well-known elimination-reverse addition−elimination of a putative cationic PdH species. However, the presence of a base is critical in eliminating this PdH species and the beneficial effect on the stereochemical outcome of the reaction has been rationalized and discussed in our previous report.[3a]

Many of the olefinic compounds prepared herein are prochiral and can be readily converted to enantiomerically pure intermediates by asymmetric catalysis. The prochiral alkenes presented in this work are conjugated systems and in

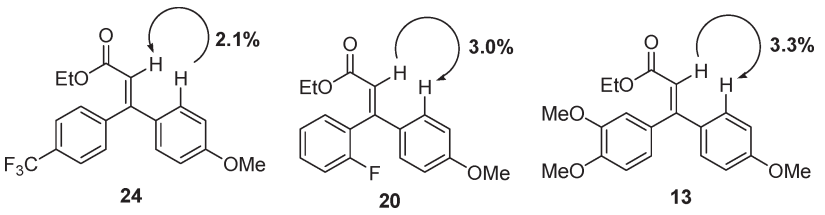
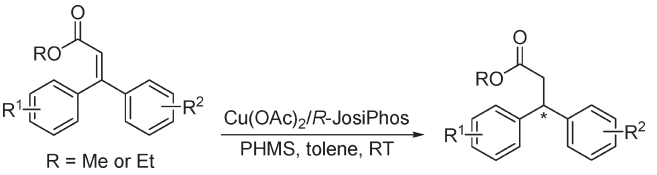


FIGURE 3. Confirmation of stereochemistry by NOE experiment.

particular, the α,β-unsaturated carbonyl compounds are capable of undergoing asymmetric 1,4 additions with a variety of nucleophiles such as copper-hydride,[12a] anilines,[12b,c] phosphorus nucleophiles,[12d] nitroalkanes,[12e] sulfur donors,[12f] organometallic reagents,[12g,h] and various enolizable carbonyl compounds.[12i,j]

The asymmetric Cu-catalyzed 1,4-hydrosilylation of α,β-unsaturated carbonyl compounds utilizes a diphosphine ligated Cu(I) hydride species generated *in situ* from a copper salt, phosphine ligand and poly(hydroxymethylsiloxane). When the reaction is quenched with a proton source, for example, alcohol, β,β-saturated carbonyl compounds are usually obtained in high optical purity.[12a] The stereochemical purity of the olefins employed in this reaction is critical to its success as the other stereoisomer will give the opposite enantiomer.[13] The modern racemic version of this methodology was pioneered by Stryker,[14a−d] and used by Buchwald[14e] for the first asymmetric 1,4 addition of Cu−H to β,β-disubstituted alkenyl substrates including α,β-unsaturated esters using *p*-tol-BINAP as ligand. Further developments were achieved by the group of Lipshutz[12] in which ligands of the SEGPHOS and JOSIPHOS families of nonracemic bis-phosphines were evaluated for the 1,4-reduction of β,β-disubstituted enoates and found to exert a high degree of facial selectivity to provide the corresponding propanoates.[15] However, both reports lack examples of 1,4-reductions with β,β-diaryl α,β-unsaturated esters, presumably due to the unavailability of a convenient and stereoselective methodology for their preparation. To further demonstrate the utility of the HM reaction, a few Heck adducts synthesized in geometrically pure form were selected for evaluation in the asymmetric Cu-catalyzed 1,4-hydrosilylation reaction. Using $Cu(OAc)_2$ (3 mol %) and *R*-JOSIPHOS as ligand (JOSIPHOS = (*R*)-1-[(*S*)-2-diphenylphosphino) ferrocenyl]ethyldicyclohexylphosphine) in the presence of excess polymethylhydrosiloxane (PMHS), the enantioselective synthesis of β,β-diaryl propanoates was investigated (Table 3).

TABLE 3. Enantioselective Conjugate Reduction of β,β-Diaryl-substituted α,β-Unsaturated Esters[a]



entry	R^1	R^2	product	yield/%[b]	ee/%[c,d]
1	H	3,4-Cl	**29**	96	89 (−)
2	4-CF_3	4-OMe	**30**	77	90 (+)
3	3,4-Me	4-OMe	**31**	96	91 (−)
4	4-Cl	4-OMe	**32**	94	90 (+)
5	3,4-OMe	4-OMe	**33**	22[e]	72
6	2,4,5-OMe	4-OMe	**34**	NR[f]	–

[a]Typical reaction conditions: β,β-diaryl enoate (0.50 mmol), $Cu(OAc)_2$ (3 mol %), *R*-JosiPhos (4 mol %), PMHS (4 equiv), ^{t}BuOH (4 equiv), toluene (3 mL), 25 °C, 16 h. [b]Corresponds to isolated yields after purification by column chromatography. [c]Determined by chiral HPLC. For details see Supporting Information. [d]Optical rotations are shown in parentheses. [e]Result corresponds to % conversion as determined by ^{1}H NMR integration. [f]No reaction observed.

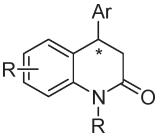


FIGURE 4. The basic structure of 4-Aryl-3,4-dihydroquinolin-2-ones.

Initially, the Cu-catalyzed asymmetric hydrosilylation protocol was applied to the synthesis of **29** to evaluate a substrate bearing an electron-withdrawing group. Employing 3 mol % $Cu(OAc)_2$ and 4 mol % of *R*-JOSIPHOS in the presence of PHMS yielded saturated ester **29** at ambient temperature in high yield and with good enantioselectivity (entry 1). Accordingly, substrates bearing electron-neutral or −withdrawing substituents on one of the phenyl rings were converted to the corresponding propanoates with similar enantioselectivities (entries 2 to 4) whereas a drop in ee was observed in the case of compound **33** (entry 5) bearing only electron donating groups. This result indicates that electronic factors can indeed influence the enantioselectivity of the process. It is also noteworthy that high conversions were difficult to achieve in the case of substrate **13** and that no reaction was observed for even more electron rich substrates (entry 6). Products **30**−**33** are novel compounds and no attempts were made to determine their absolute configuration. However, it was possible to assign the absolute

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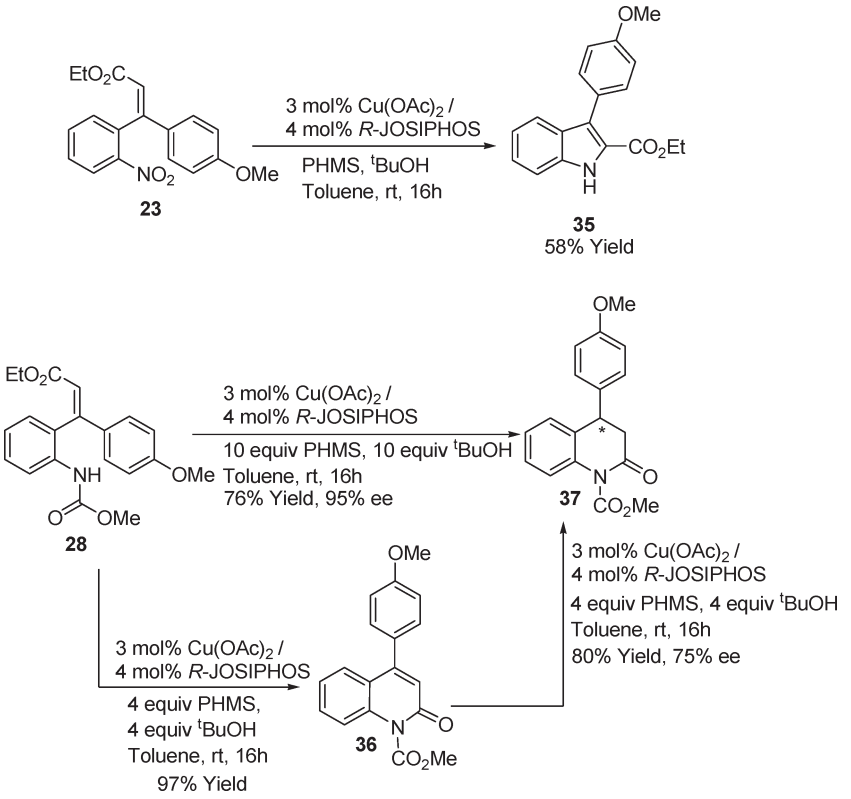
(14) (a) Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, *29*, 3749. (b) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. (c) Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1989**, *30*, 5677. (d) Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 3237. (e) Appella, D. H. L.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473.

(15) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126* (27), 8352.

(16) Quallich, G. J. U.S. Patent 5196607, March 23, 1993.

SCHEME 3. Synthesis of a 3-Aryl Indole and a 4-Aryl-dihydroquinolinone from Heck Adducts



stereochemistry of **29** (*S*-enantiomer) by comparison of its optical rotation with the literature value.[16]

These promising results prompted us to explore the application of this chemistry for the preparation of a chiral 4-aryl-2-quinolinone derivative (Figure 4), a class of compounds salient in many biologically active compounds.[17] There are precedents in the literature for the asymmetric synthesis of 4-aryl-2-quinolinones, the first being the utilization of dynamic thermodynamic resolution of dilithioaniline to prepare enantioenriched tetrahydroquinoline derivatives.[18a] An alternative approach involves the asymmetric conjugate addition of aryl boronic acid nucleophiles to electron-deficient acceptors catalyzed by a Rh-diene complex.[18b] The *ortho*-nitro adduct was subjected to hydrogenation (H_2, Pd/C in MeOH) to afford the desired lactam in high yield and ee.[18b] We envisaged that the target compound could be prepared via a process involving a HM reaction followed by asymmetric 1,4 reduction and finally an intramolecular carbon−nitrogen bond-forming step.

To extend the utility of HM methodology, we then decided to take advantage of the functional groups present in compounds **23** and **28** for subsequent elaboration (Scheme 3).

Initially, the Cu-catalyzed 1,4 reduction of **23** was attempted using the aforementioned conditions, but surprisingly, indole **35** was isolated instead of the expected β,β-diaryl propanoate. The structure of **35** was evidenced by a sharp low field signal in the ^{1}H NMR (10.71 ppm). Furthermore, its spectral data were consistent with those reported in the literature[19] and mass spectrometry confirmed its molecular identity. This result implies that nitro groups in the *ortho* position may be incompatible with this methodology and we tentatively propose that the enolate initially formed from addition of Cu−H may have undergone an intramolecular nucleophilic substitution with the nitro group. To circumvent formation of the indole structure, we attempted the reduction of **28** using the same protocol, but once again our target compound evaded us and we instead isolated the unsaturated lactam **36** in almost quantitative yield. Interestingly, an intramolecular amidation reaction took place in preference to the 1,4 reduction but we were pleased to find that this intermediate could be subjected to a second Cu-catalyzed 1,4-reduction to provide **37** in a yield of 80% and with 75% ee. A control reaction subjecting **28** to $Cu(OAc)_2$, *R*-JOSIPHOS and ^{t}BuOH and another control using only 4 equivalents of PHMS in toluene were carried out, but the substrate was recovered and no cyclization was observed. This result implies that formation of **36** occurs only under catalytic conditions and we speculated that **37** was not afforded directly in the first instance due to an insufficient supply of the hydrosiloxane polymer. Also, upon

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(18) (a) Kim, Y.; Shin, E.; Beak, P.; Park, Y. S. *Synthesis* **2006**, *22*, 3805. (b) Paquin, J.-F.; Steptenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821.

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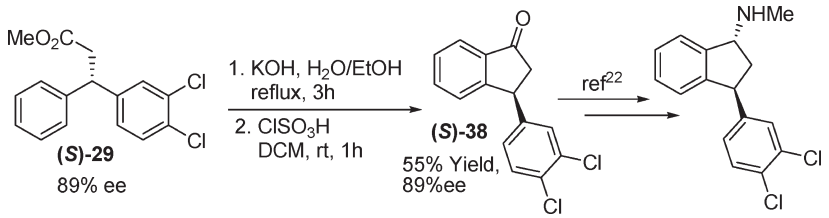
SCHEME 4. Enantioselective Formal Synthesis of (−)-Indatraline



cyclization, an ethoxide anion is liberated and may possibly be responsible for deactivation of the catalyst or the poly(hydroxymethylsiloxane), thus preventing the formation of Cu−H. The synthesis of **37** was therefore reattempted but using 10 equivalents of both PHMS and ^{t}BuOH yielding the expected dihydroquinoline-2-one **37** in good yield and surprisingly with higher ee than that obtained from substrate **36**.

We have previously shown that saturated β,β-diarylated product **29** could be employed in a concise formal total syntheses of (±)-Indatraline.[3a,20] One of our objectives was to take advantage of the high degree of stereoselectivity of this process and to explore the formal asymmetric synthesis of Indatraline. Hitherto, only one catalytic enantioselective synthesis of (+)-Indatraline has been reported and this strategy utilized an enantioselective rhodium-catalyzed carbenoid C−H insertion reaction as the key step.[21] More recently, a series of α,β-unsaturated nitriles were reduced enantioselectively by a copper−Josiphos catalyst in the presence of hydrosilane and applied to the enantioselective formal synthesis of (−)-Indatraline.[13] The enantioselectivity for the saturated nitrile intermediate was reported as 96% (*S*-enantiomer), but the optical purity for the cyclic indanone intermediate which is a key intermediate in the synthesis of Indatraline,[22] was not disclosed. A complementary approach to the key cyclic indanone intermediate **38**, from the β,β-diarylated propanoate **29** is shown above (Scheme 4).

Hydrolysis of the ester function with aqueous KOH and subsequent cyclization using chlorosulfonic acid afforded the known precursor **38** in 55% yield over 2 steps. More importantly, we have demonstrated that the optical purity of **29** does not decrease during the hydrolysis and cyclization processes.

Conclusion

We have shown that Pd-catalyzed HM reaction is a highly useful method for the formation of unsymmetrical β,β-diarylacrylates in excellent stereoselectivity. Trisubstituted olefins with aryl groups having a variety of electronic and steric properties were prepared in good to excellent yields. In general, electronically rich cinnamate esters were more reactive substrates in the HM reaction and coupling of electron deficient alkenes with arenediazonium salts proved to be more challenging. Notably, formation of a single geometric isomer could be guaranteed by simply conducting the reaction in the presence of a base and thus further corroborates the hypothesis of isomerization of the Heck adduct by a PdH readdition. Other advantages that this methodology presents include the mild reaction conditions, the fact that they can be easily carried out under aerobic conditions and that they are often fast, requiring only a few hours to go to completion. The ease of preparation of the olefin substrates renders this methodology an attractive alternative to the Cu-catalyzed conjugate addition of arylboronic acids to alkynoates. Thus, the present methodology has demonstrated broad scope and permitted structural diversity in the synthesis of unsymmetrical β,β-diarylacrylates derivatives.

The methodological potential of the present technique was demonstrated by the asymmetric Cu-catalyzed 1,4 reduction of the Heck adducts to the corresponding β,β-diarylated saturated esters with high enantioselectivities. In one isolated example, we observed the formation of an 3-aryl indole during the attempted Cu-catalyzed 1,4-reduction of the *ortho*-nitro Heck adduct **23** which presumably proceeded by an intramolecular cyclization between a copper-enolate and the nitro group. Finally, we have successfully combined a highly stereo and enantioselective catalytic methodology toward the asymmetric formal synthesis of (−)-Indatraline and to a chiral 4-aryl-3,4-dihydroquinolin-2-one.

Experimental Section

General Procedure for the Heck Arylation of Cinnamate Esters. A test tube (inside diameter 13 mm; length 100 mm), equipped with a magnetic stir bar was charged with cinnamate ester (0.5 mmol), $Pd(OAc)_2$, (0.025 mmol), base (when used, 1.5 mmol) and solvent (3 mL). After vigorous stirring at room temperature for 30 s, the diazonium salt (1.0 mmol) was added in one portion and the reaction left to stir until complete consumption of the starting material was indicated by TLC (Thin Layer Chromatography). Upon completion, the reaction mixture was concentrated under reduced pressure and loaded directly onto silica gel (using a small amount of DCM to transfer the oily residue) and chromatographed with ethyl acetate−hexanes to give the desired Heck-adducts.

(*Z*)-Methyl 3-(4-chlorophenyl)-3-(4-methoxyphenyl)acrylate (6). Product obtained as a pale-yellow oil (77% yield). R_f = 0.20 (Hexanes/EtOAc, 9:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 3001, 2838, 1721, 1601, 1571, 1511, 1489, 1462, 1433, 1369, 1363, 1293, 1275, 1253, 1163, 1090, 1032, 1014, 974, 880, 832, 763; δ_H (250 MHz, $CDCl_3$): 7.39 (2H, d, *J* 9.0), 7.13−7.26 (4H, m), 6.87 (2H, d, *J* 9.0), 6.32 (1H, s), 3.82 (3H, s), 3.62 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 166.4, 160.9, 155.7, 137.4, 134.1, 132.7, 130.5, 129.7, 128.2, 115.0, 113.8, 55.4, 51.2; MS *m*/*z* (EI): calcd for $C_{17}H_{15}ClO_3$ 302.0710, found 302.0729.

Methyl-3-methoxy-2-(3,4,5-trimethoxyphenyl)-3-(4-methoxyphenyl)propanoate (9). Product obtained as a white solid (53% yield). mp. 118−119 °C; R_f = 0.18 (Hexanes/EtOAc, 4:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 2946, 1732,

(20) Indatraline (Lu 19−005) is a potent psychoactive compound with high binding and inhibitory activity for neuronal monoamine reuptake sites, including dopamine and serotonin transporters and is currently being investigated as medication to treat cocaine addiction. For further information, see: (a) Bogeso, K. P.; Christensen, A. V.; Hyttel, J.; Liljefors, T. *J. Med. Chem.* **1985**, *28*, 1817. (b) Hyttel, J.; Larsen, J. *J. Neurochem.* **1985**, *44*, 1615. (c) Arnt, J.; Christensen, A. V.; Hyttel, J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1985**, *329*, 101. (d) Hurd, Y. L.; Ungerstedt, U. *Eur. J. Pharmacol.* **1989**, *166*, 251. (e) Negus, S. S.; Brandt, M. R.; Mello, N. K. *J. Pharmacol. Exp. Ther.* **1999**, *291*, 60–69.

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1723, 1609, 1590, 1510, 1461, 1424, 1370, 1325, 1306, 1281, 1245, 1192, 1179, 1159, 1125, 1097, 1070, 1034, 1015, 971, 928, 841, 829, 806, 777, 734, 706, 672, 637, 618; δ_H (250 MHz, $CDCl_3$): 6.94 (2H, d, *J* 8.5), 6.69 (2H, d, *J* 8.5), 6.23 (2H, s), 4.55 (1H, d, *J* 10.5), 3.76 (3H, s), 3.74 (3H, s), 3.72 (3H, s), 3.69 (6H, s), 3.21 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 173.1, 159.3, 152.8, 137.3, 130.3, 130.2, 128.5, 113.4, 105.8, 85.5, 60.7, 59.5, 56.8, 56.0, 55.1, 52.1; MS *m*/*z* (EI): calcd for $C_{21}H_{26}O_7$ 390.1679, found 358.1412 (corresponds to expected mass of 390.1679 minus a molecule of MeOH lost under GC-HRMS (EI) conditions; therefore, the calcd value would be 358.1416).

(*E*)-Methyl 3-(2-Methoxyphenyl)-3-(4-methoxyphenyl)acrylate (11). Product obtained as a pale-yellow oil (42% yield). R_f = 0.17 (Hexanes/EtOAc, 5:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 3000, 1721, 1605, 1576, 1511, 1489, 1462, 1434, 1362, 1292, 1249, 1164, 1112, 1028, 971, 880, 834, 807, 788, 755, 736; δ_H (250 MHz, $CDCl_3$): 7.10−7.19 (3H, m), 6.81−6.95 (5H, m), 6.18 (1H, s), 3.81 (3H, s), 3.65 (3H, s), 3.64 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 166.9, 159.4, 157.3, 154.2, 131.4, 131.0, 130.3, 129.9, 120.3, 118.8, 113.7, 112.8, 111.6. 55.6, 55.1, 51.2; MS *m*/*z* (EI): calcd for $C_{18}H_{18}O_4$ 298.1205, found 298.1223.

(*E*)-Methyl 3-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)acrylate (12). Product obtained as a pale-yellow oil (76% yield). R_f = 0.15 (Hexanes/EtOAc, 4:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 3001, 2951, 2837, 1721, 1606, 1597, 1579, 1513, 1463, 1441, 1417, 1365, 1324, 1289, 1230, 1222, 1173, 1162, 1137, 1027, 977, 920,, 839, 812, 768, 733, 702; δ_H (250 MHz, $CDCl_3$): 7.14 (2H, d, *J* 9.0), 6.80−6.93 (5H, m), 6.24 (1H, s), 3.89 (3H, s), 3.85 (3H, s), 3.83 (3H, s), 3.63 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 170.0, 159.7, 157.0, 150.4, 148.7, 134.1, 130.9, 128.6, 122.2, 114.5, 113.2, 113.3, 110.6, 55.9, 55.8, 55.2, 51.1; MS *m*/*z* (EI): calcd for $C_{19}H_{20}O_5$ 328.1311, found 328.1293.

(*Z*)-Ethyl 3-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)acrylate (13). Product obtained as a pale-yellow oil (99% yield). R_f = 0.12 (Hexanes/EtOAc, 4:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 2910, 1716, 1599, 1513, 1463, 1419, 1368, 1353, 1321, 1292, 1253, 1232, 1175, 1156, 1135, 1095, 1028, 834, 810, 766; δ_H (250 MHz, $CDCl_3$): 7.23 (2H, d, *J* 8.75), 6.78−6.91 (4H, m), 6.70 (1H, d, *J* 2.0), 6.23 (1H, s), 4.02 (2H, q, *J* 7.0), 3.91 (3H, s), 3.80 (6H, s), 1.10 (3H, t, *J* 7.0); δ_C (62.5 MHz, $CDCl_3$): 166.4, 160.7, 156.0, 149.1, 148.3, 133.5, 131.6, 129.9, 122.2, 115.1, 113.7, 112.8, 110.4, 59.8, 55.9, 55.8, 55.3, 14.1; MS *m*/*z* (EI): calcd for $C_{20}H_{22}O_5$ 342.1467, found 342.1472.

(*Z*)-Ethyl 3-(2,4,5-Trimethoxyphenyl)-3-(4-methoxyphenyl)acrylate (14). Product obtained as a pale-yellow oil (96% yield). R_f = 0.26 (Hexanes/EtOAc, 3:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 2936, 1719, 1601, 1573, 1511, 1464, 1441, 1420, 1397, 1366, 1351, 1251, 1215, 1207, 1171, 1156, 1113, 1033, 862, 834, 735; δ_H (250 MHz, $CDCl_3$): 7.28 (2H, d, *J* 9.0), 6.82 (2H, d, *J* 9.0), 6.57 (1H, s), 6.55 (1H, s), 6.35 (1H, s), 4.02 (2H, q, *J* 7.0), 3.90 (3H, s), 3.77 (3H, s), 3.75 (3H, s), 3.65 (3H, s), 1.09 (3H, t, *J* 7.0); δ_C (62.5 MHz, $CDCl_3$): 166.1, 160.6, 151.9, 1512.1, 149.5, 142.9, 132.8, 129.0, 119.8, 116.3, 113.9, 113.7, 98.0, 59.7, 56.8, 56.5, 55.9, 55.2, 14.1; MS *m*/*z* (EI): calcd for $C_{21}H_{24}O_6$ 372.1573, found 372.1587.

(*Z*)-Methyl 3-(4-Methoxyphenyl)-3-(4-nitrophenyl)acrylate (15). Product obtained as a pale-yellow solid after evaporation of the volatiles (96% yield). mp. 88−89 °C; R_f = 0.31 (Hexanes/EtOAc, 9:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 3080, 3001, 2839, 1725, 1606, 1514, 1491, 1460, 1434, 1410, 1347, 1297, 1250, 1168, 1154, 1110, 1032, 973, 912, 872, 854, 834, 803, 762, 732; δ_H (250 MHz, $CDCl_3$): 8.19 (2H, d, *J* 9.0), 7.47 (2H, d, *J* 9.0), 7.15 (2H, d, *J* 9.0), 6.94 (2H, d, *J* 9.0), 6.33 (1H, s), 3.85 (3H, s), 3.66 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 166.0, 160.2, 154.2, 148.1, 147.9, 130.9, 129.5, 129.4, 123.6, 119.2, 113.6, 55.3, 51.6; MS *m*/*z* (EI): calcd for $C_{17}H_{15}NO_5$ 313.0950, found 313.0964.

(*Z*)-Methyl 3-(4-bromophenyl)-3-(4-methoxyphenyl)acrylate (16). Product obtained as a pale-yellow oil (84% yield). R_f = 0.46 (Hexanes/EtOAc, 4:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 3007, 1721, 1600, 1587, 1570, 1510, 1486, 1462, 1433, 1391, 1364, 1293, 1274, 1252, 1215, 1178, 1162, 1069, 1032, 1011, 973, 880, 832, 759; δ_H (250 MHz, $CDCl_3$): 7.51 (2H, d, *J* 8.5), 7.20 (2H, d, *J* 9.0), 7.07 (2H, d, *J* 8.5), 6.83 (2H, d, *J* 9.0), 6.32 (1H, s), 3.82 (3H, s), 3.62 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 166.4, 161.0, 155.7, 138.0, 132.6, 131.1, 130.8, 129.7, 122.4, 115.0, 113.9, 55.4, 51.2; MS *m*/*z* (EI): calcd for $C_{17}H_{15}BrO_3$ 346.0205, found 346.0216.

(*E*)-Methyl 3-(4-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylate (17). Product obtained as a pale-yellow oil (49% yield). R_f = 0.31 (Hexanes/EtOAc, 9:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 3001, 2837, 1721, 1593, 1515, 1489, 1463, 1434, 1418, 1363, 1325, 1291, 1265, 1223, 1163, 1136, 1088, 1024, 920, 853, 810, 766, 735; δ_H (250 MHz, $CDCl_3$): 7.39 (2H, d, *J* 8.5), 7.17 (2H, d, *J* 8.5), 6.77−6.84 (3H, m), 6.32 (1H, s), 3.89 (3H, s), 3.83 (3H, s), 3.62 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 166.3, 155.9, 150.6, 148.8, 137.3, 134.2, 132.9, 130.6, 128.1, 122.1, 115.2, 110.7, 110.6, 55.9, 55.9, 51.3; MS *m*/*z* (EI): calcd for $C_{18}H_{17}ClO_4$ 332.0815, found 332.0817.

(*Z*)-Methyl 3-(3-Chlorophenyl)-3-(4-methoxyphenyl)acrylate (18). Product obtained as a pale-yellow oil (72% yield). R_f = 0.20 (Hexanes/EtOAc, 9:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 2949, 1723, 1601, 1569, 1511, 1463, 1433, 1360, 1294, 1274, 1254, 1181, 1156, 1119, 1094, 1078, 1032, 977, 874, 833, 811, 795, 772, 737, 700; δ_H (250 MHz, $CDCl_3$): 7.19−7.36 (5H, m), 7.09−7.12 (1H, m), 6.84 (2H, d, *J* 9.0), 6.33 (1H, s), 3.82 (3H, s), 3.61 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 166.2, 161.0, 155.2, 140.8, 133.8, 132.3, 129.7, 129.2, 128.9, 128.2, 127.3, 115.2, 113.9, 55.4, 51.3; MS *m*/*z* (EI): calcd for $C_{17}H_{15}ClO_3$ 302.0710, found 302.0718.

(*Z*)-Methyl 3-(3,4-Dichlorophenyl)-3-(4-methoxyphenyl)acrylate (19). Product obtained as a pale-yellow oil (78% yield). R_f = 0.36 (Hexanes/EtOAc, 4:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 2838, 1721, 1601, 1571, 1551, 1511, 1469, 1433, 1376, 1360, 1295, 1276, 1254, 1159, 1127, 1031, 979, 876, 833, 816, 759; δ_H (250 MHz, $CDCl_3$): 7.47−7.48 (1H, m), 7.28 (1H, d, *J* 2.0), 7.19 (2H, d, *J* 9.0), 7.04 (1H, dd, *J* 4.0, 8.0), 6.84 (2H, d, *J* 9.0), 6.33 (1H, s), 3.82 (3H, s), 3.63 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 166.1, 161.2, 154.3, 139.0, 132.2, 132.2, 132.0, 130.9, 129.9, 129.7, 128.6, 115.5, 114.0, 55.4, 51.3; MS *m*/*z* (EI): calcd for $C_{17}H_{14}Cl_2O_3$ 336.0320, found 336.0299.

(*Z*)-Ethyl 3-(2-Fluorophenyl)-3-(4-methoxyphenyl)acrylate (20). Product obtained as a pale-yellow oil (48% yield). R_f = 0.32 (Hexanes/EtOAc, 8:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 2980, 1719, 1624, 1600, 1574, 1512, 1490, 1462, 1449, 1420, 1368, 132, 1254, 1221, 1159, 1117, 1099, 1021, 876, 8345, 793, 760; δ_H (250 MHz, $CDCl_3$): 7.33−7.44 (1H, m), 7.26 (2H, d, *J* 9.0), 7.09−7.21 (3H, m), 6.84 (2H, d, *J* 9.0), 6.84 (2H, d, *J* 9.0), 6.46 (1H, s), 4.03 (2H, q, *J* 7.0), 3.81 (3H, s), 1.13 (3H, t, *J* 7.0); δ_C (62.5 MHz, $CDCl_3$): 165.6, 161.5 (d, *J* 245), 160.9, 149.4, 131.8, 130.7 (d, *J* 3.4), 129.8 (d, *J* 8.1), 129.0, 126.9 (d, *J* 16.4), 123.7 (d, *J* 3.5), 117.2, 115.5 (d, *J* 21.9), 113.9, 59.9, 55.3, 14.0; δ_F (235 MHz, $CDCl_3$): −115.0; MS *m*/*z* (EI): calcd for $C_{18}H_{17}FO_3$ 300.1162, found 300.1157.

(*Z*)-Methyl 3-(4-Chlorophenyl)-3-(4-nitrophenyl)acrylate (21). Product obtained as a pale-yellow oil (65% yield). R_f = 0.31 (Hexanes/EtOAc, 9:1); υ_{max} (thin film, cm^{-1}): 3086, 1726, 1623, 1596, 1520, 1490, 1434, 1408, 1346, 1271, 1260, 1193, 1169, 1107, 1090, 1013, 973, 874, 854, 830, 760, 737, 699; δ_H (250 MHz, $CDCl_3$): 8.21 (2H, d, *J* 9.0), 7.38−7.45 (4H, m), 7.16 (2H, d, *J* 8.5), 6.43 (1H, s), 3.66 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 165.5, 153.0, 148.2, 146.6, 135.8, 135.0, 130.5, 129.1, 128.6, 123.7, 120.4, 51.7; MS *m*/*z* (EI): calcd for $C_{16}H_{12}ClNO_4$ 317.0455, found 317.0471.

(*Z*)-Methyl 3-(3-Chlorophenyl)-3-(4-nitrophenyl)acrylate (22). Product obtained as a pale-yellow oil (25% yield). R_f = 0.20 (Hexanes/EtOAc, 9:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 2922, 1728, 1615, 1594, 1564, 1514, 1474, 1433, 1344, 1271, 1254, 1192, 1166, 1080, 1009, 972, 869, 851, 792, 760, 739; δ_H (250 MHz, $CDCl_3$): 8.18 (2H, d, *J* 9.0), 7.36−7.46 (4H, m), 7.17−7.19 (4H, m), 7.08 (1H, dt, *J* 1.8 7.0), 6.84 (2H, d, *J* 9.0), 6.33 (1H, s), 3.82

(3H, s), 3.61 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 165.4, 152.6, 146.2, 139.2, 134.3, 129.6, 129.0, 128.9, 128.3, 127.2, 124.4, 123.8, 120.7, 51.7; MS *m*/*z* (EI): calcd for $C_{16}H_{11}ClNO_4$ 317.0455, found 317.0479.

(*Z*)-Ethyl 3-(4-Methoxyphenyl)-3-(2-nitrophenyl)acrylate (23). Product obtained as a white solid after recrystallization with ethyl acetate/hexanes (73% yield). mp. 96−98 °C, R_f = 0.13 (Hexanes/EtOAc, 4:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 2981, 1715, 1638, 1601, 1572, 1525, 1513, 1456, 1443, 1367, 1346, 1291, 1273, 1253, 1179, 1031, 975, 856, 834, 787; δ_H (250 MHz, $CDCl_3$): 8.19 (1H, d, *J* 9.5), 7.66 (1H, t, *J* 7.5), 7.58 (1H, t, *J* 7.5), 7.27−7.29 (3H, m), 6.85 (2H, d, *J* 9.0), 6.43 (1H, s), 3.97 (2H, q, *J* 7.5), 3.82 (3H, s), 1.10 (3H, t, *J* 7.5); δ_C (62.5 MHz, $CDCl_3$): 165.9, 161.2, 153.2, 148.2, 135.6, 133.4, 131.3, 130.9, 129.2, 128.9, 124.8, 115.2, 114.3, 60.3, 55.6, 19.2; MS *m*/*z* (EI): calcd for $C_{18}H_{17}NO_5$ 327.1107, found 327.1100.

(*E*)-Ethyl 3-(4-(Trifluoromethyl)phenyl)-3-(4-methoxyphenyl)-acrylate (24). Product obtained as a pale-yellow oil (91% yield). R_f = 0.38 (Hexanes/EtOAc, 9:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 2981, 1761, 1791, 1600, 1573, 1510, 1464, 1443, 1420, 1407, 1370, 1325, 1296, 1254, 1164, 1125, 1066, 1020, 876, 703, 623; δ_H (250 MHz, $CDCl_3$): 7.64 (2H, d, *J* 8.0), 7.31 (2H, d, *J* 8.0), 7.19 (2H, d, *J* 9.0), 6.84 (2H, d, *J* 9.0), 6.34 (1H, s), 4.03 (2H, q, *J* 7.0), 3.83 (3H, s), 1.11 (3H, t, *J* 7.0); δ_C (62.5 MHz, $CDCl_3$): 165.9, 161.1, 154.7, 143.1, 132.2, 129.6, 129.4, 124.7 (q, *J* 3.8), 116.0, 113.9, 60.1, 55.3, 13.9; δ_F (235 MHz, $CDCl_3$): −62.5; MS *m*/*z* (EI): calcd for $C_{19}H_{17}F_3O_3$ 350.1130, found 350.1142.

(*Z*)-Methyl 3-(4-Methoxyphenyl)-3-*o*-tolylacrylate (25). Product obtained as a pale-yellow oil (73% yield). R_f = 0.37 (Hexanes/EtOAc, 4:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 3013, 2838, 1724, 1702, 1598, 1571, 1511, 1435, 1359, 1254, 1182, 1118, 1032, 973, 834, 762, 732; δ_H (250 MHz, $CDCl_3$): 7.26−7.29 (5H, m), 7.04−7.07 (1H, m), 6.83 (2H, d, *J* 9.0), 6.48 (1H, s), 3.81 (3H, s), 3.59 (3H, s), 2.09 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 166.2, 160.9, 156.2, 138.7, 135.3, 131.6, 129.8, 128.9, 128.2, 127.7, 125.4, 114.6, 114.0, 55.3, 51.1, 19.5; MS *m*/*z* (EI): calcd for $C_{18}H_{18}O_3$ 282.1256, found 282.1276.

(*Z*)-Methyl 3-(4-Nitrophenyl)-3-*o*-tolylacrylate (26). Product obtained as a pale-yellow oil (54% yield). R_f = 0.13 (Hexanes/EtOAc, 9:1); υ_{max} (thin film, cm^{-1}): 3019, 1729, 1624, 1594, 1519, 1457, 1435, 1409, 1345, 1263, 1192, 1169, 1110, 1013, 973, 851, 767, 761, 731, 697; δ_H (250 MHz, $CDCl_3$): 8.15 (2H, d, *J* 9.0), 7.45 (2H, d, *J* 9.0), 7.26−7.33 (3H, m), 7.05−7.08 (1H, m), 6.60 (1H, s), 3.62 (3H, s), 2.06 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 165.4, 153.8, 148.2, 145.6, 137.1, 130.2, 128.5, 125.8, 123.8, 120.5, 114.0, 51.6, 19.6; MS *m*/*z* (EI): calcd for $C_{17}H_{15}NO_4$ 297.1001, found 297.0984.

(*Z*)-Ethyl 3-(4-Methoxyphenyl)-3-(3,4-dimethylphenyl)acrylate (27). Product obtained as a pale-yellow solid (91% yield). mp. 55−56 °C; R_f = 0.29 (Hexanes/EtOAc, 5:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 2976, 1720, 159, 1572, 1522, 1461, 1420, 1367, 1352, 1252, 1177, 1154, 1119, 1035, 873, 833; δ_H (250 MHz, $CDCl_3$): 7.13−7.28 (3H, m), 6.95−6.98 (2H, m), 6.82 (2H, d, *J* 9.0), 6.26 (1H, s), 4.02 (2H, q, *J* 7.0), 3.82 (3H, s), 2.31 (3H, s), 2.26 (3H, s), 1.12 (3H, t, *J* 7.0); δ_C (62.5 MHz, $CDCl_3$): 166.4, 160.7, 156.7, 136.6, 136.5, 135.9, 133.9, 130.2, 129.8, 129.1, 126.7, 115.0, 113.7, 59.9, 55.3, 19.8, 19.7, 14.0; MS *m*/*z* (EI): calcd for $C_{20}H_{22}O_3$ 310.1569, found 310.1560.

Methyl-2-((*Z*)-2-(ethoxycarbonyl)-1-(4-methoxyphenyl)vinyl)-phenylcarbamate (28). Product obtained as viscous a pale-yellow oil (87% yield). R_f = 0.36 (Hexanes/EtOAc, 4:1); υ_{max} (thin film, cm^{-1}): 3306, 1728, 1696, 1633, 1579, 1530, 1476, 1456, 1367, 1324, 1301, 1283, 1266, 1235, 1137, 1105, 1063, 1031, 992, 882, 862, 832, 759, 733, 713; δ_H (250 MHz, $CDCl_3$): 7.99 (1H, d, *J* 7.8), 7.35 (1H, t, *J* 8.5), 7.26 (2H, d, *J* 7.5), 7.08 (1H, t, *J* 7.3), 6.99 (1H, dd, *J* 1.5 7.5), 6.83 (2H, d, *J* 9.0), 6.54 (1H, s), 6.52 (1H, br s), 3.98 (2H, q, *J* 7.5), 3.80 (3H, s), 3.65 (3H, s), 1.05 (3H, t, *J* 7.5); δ_C (62.5 MHz, $CDCl_3$): 165.7, 161.2, 154.0, 151.4, 135.1, 130.6, 129.0, 128.9, 128.8, 123.5, 117.2, 114.2, 60.3, 55.4, 52.2, 13.9; MS *m*/*z* (EI): calcd for $C_{20}H_{21}NO_5$ 355.1420, found 355.1432.

General Procedure for the Copper-Catalyzed Enantioselective Reduction of *β*,*β*-Diarylacrylates. $Cu(OAc)_2$ (0.015 mmol) and (*R*)-1-[(*S*)-2-diphenylphosphino) ferrocenyl]ethyldicyclohexylphosphine) (0.020 mmol) were placed in an oven-dried Schlenk tube and the air evacuated and backfilled with nitrogen four times. Next, anhydrous toluene (0.5 mL) was added and the reaction mixture was stirred for 15 min at room temperature. Polymethylhydrosiloxane (2.0 mmol) was added and the reaction was stirred for a further 5 min for catalyst activation. The unsaturated ester (0.5 mmol) in toluene (1.0 mL) was added, followed by ^tBuOH (2.0 mmol). The reaction was sealed, and stirred overnight at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ (5 mL) and transferred to a round-bottomed flask with the aid of EtOAc (5 mL). The biphasic mixture was stirred vigorously for one hour. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash chromatography on silica gel.

(*S*)-Methyl 3-(3,4-Dichlorophenyl)-3-phenylpropanoate (29). Product obtained as a colorless viscous oil (96% yield). R_f = 0.24 (Hexanes/EtOAc, 9:1); δ_H (250 MHz, $CDCl_3$): 7.18−7.36 (7H, m), 7.06 (1H, dd, *J* 1.8, 8.3), 4.48 (1H, t, *J* 8.0), 3.61 (3H, s), 3.02 (2H, d, *J* 8.0). NMR data were consistent with the literature values.[3a] The ee (89% ee) was measured by chiral HPLC on an OD column (^iPrOH/hexane 1:99 to 15:85 over 10 min then 15:85 for 6 min, 0.8 mL/min, λ = 235 nm): (*S*)-enantiomer t_r = 10.44 min and (*R*)-enantiomer t_r = 13.44 min. $[\alpha]_D^{20}$ −1.0 (*c* 1.2, DCM) [lit.[16] value for the *R* enantiomer:$[\alpha]_D^{20}$ +1.6 (*c* 10.6, DCM).

(+)-Ethyl 3-(4-(Trifluoromethyl)phenyl)-3-(4-methoxyphenyl)-propanoate (30). Product obtained as a colorless viscous oil (77% yield). R_f = 0.22 (Hexanes/EtOAc, 9:1); υ_{max} (thin film, cm^{-1}): 2982, 2838, 1733, 1617, 1584, 1512, 1464, 1443, 1418, 1392, 1372, 1326, 1304, 1251, 1214, 1163, 1121, 1069, 1035, 1018, 964, 903, 878, 827, 810, 754; δ_H (250 MHz, $CDCl_3$): 7.54 (2H, d, *J* 8.0), 7.36 (2H, d, *J* 8.0), 7.15 (2H, d, *J* 8.5), 6.82 (2H, d, *J* 8.5), 4.53 (1H, t, *J* 8.0), 4.02 (2H, q, *J* 7.0), 3.77 (3H, s), 3.01 (2H, d, *J* 8.0), 1.10 (3H, t, *J* 7.0); δ_C (62.5 MHz, $CDCl_3$): 171.4, 158.4, 147.9, 134.6, 128.6, 127.9, 125.4 (q, *J* 3.9), 122.3, 114.4, 114.1, 60.5, 55.2, 46.1, 40.6, 14.0; MS *m*/*z* (EI): calcd for $C_{19}H_{19}F_3O_3$ 352.1286, found 352.1292. The ee (90% ee) was measured by chiral HPLC on an AD-H column (^iPrOH/hexane 1:99 to 2:98 over 15 min then 10:90 over 3 min and hold at this ratio for a further 12 min, 0.8 mL/min, λ = 254 nm): (+)-enantiomer t_r = 19.18 min and (−)-isomer t_r = 20.27 min. $[\alpha]_D^{20}$ +1.0 (*c* 2.2, DCM).

(−)-Ethyl 3-(4-Methoxyphenyl)-3-(3,4-dimethylphenyl)propanoate (31). Product obtained as a colorless viscous oil (96% yield). R_f = 0.25 (Hexanes/EtOAc, 3:1); υ_{max} (thin film, cm^{-1}): 2975, 1734, 1611, 1583, 1511, 1456, 1369, 1302, 1250, 1179, 1151, 1111, 1034, 903, 832, 785; δ_H (250 MHz, $CDCl_3$): 7.16 (2H, d, *J* 8.5), 6.94−7.07 (3H, m), 6.81 (2H, d, *J* 8.5), 4.28 (1H, t, *J* 8.0), 4.01 (2H, q, *J* 7.0), 3.77 (3H, s), 2.99 (2H, d, *J* 8.0), 2.22 (3H, s), 2.21 (3H, s), 1.12 (3H, t, *J* 7.0); δ_C (62.5 MHz, $CDCl_3$): 171.9, 158.0, 141.4, 136.5, 136.0, 134.6, 129.7, 129.0, 128.6, 124.7, 113.9, 60.3, 55.2, 45.9, 41.1, 19.9, 19.3, 14.1; MS *m*/*z* (EI): calcd for $C_{20}H_{24}O_3$ 312.1725, found 312.1756. The ee (91% ee) was measured by chiral HPLC on an AD-H column (^iPrOH/hexane 1:99 to 2:98 over 15 min then 5:95 over 3 min and finally 10:90 over 11 min, 0.8 mL/min, λ = 254 nm): (−)-enantiomer t_r = 17.55 min and (+)-enantiomer t_r = 19.54 min. $[\alpha]_D^{20}$ −2.9 (*c* 4.0, DCM).

(+)-Methyl 3-(4-Chlorophenyl)-3-(4-methoxyphenyl)propanoate (32). Product obtained as a colorless viscous oil (94% yield). R_f = 0.28 (Hexanes/EtOAc, 9:1); υ_{max} (thin film, cm^{-1}): 2974, 1740, 1513, 1491, 1366, 1270, 1201, 1026, 903, 845, 783; δ_H (250 MHz, $CDCl_3$): 7.23 (2H, d, *J* 8.5), 7.10−7.17 (4H, m), 6.81 (2H, d, *J* 8.5), 4.45 (1H, t, *J* 8.0), 3.77 (3H, s), 3.59 (3H, s), 2.98 (2H, d, *J* 8.0); δ_C (62.5 MHz, $CDCl_3$): 172.1, 158.3, 142.3, 136.0, 132.3, 128.9, 128.6,

128.5, 114.0, 55.2, 51.7, 45.5, 40.6; MS *m*/*z* (EI): calcd for $C_{17}H_{17}ClO_3$ 304.0866, found 304.0867. The ee (90% ee) was measured by chiral HPLC on an AD-H column (^{i}PrOH/hexane 1:99 to 1:98 over 26 min, 0.8 mL/min, λ = 254 nm): (+)-enantiomer t_r = 11.41 min and (−)-enantiomer t_r = 13.85 min. $[\alpha]_D^{20}$ +0.4 (*c* 4.2, DCM).

Methyl 3-(4-Chlorophenyl)-3-(4-methoxyphenyl)propanoate (33). Obtained as an inseparable mixture of starting material and product after column chromatography. Conversion of 22% as determined by ^{1}H NMR integration by comparison of the methine triplet (4.45 ppm) corresponding to **33** and the olefinic hydrogen singlet (6.24 ppm) of **14** (see Supporting Information for ^{1}H NMR spectra). MS *m*/*z* (EI): calcd for $C_{20}H_{24}O_5$ 344.1624, found 344.1646. The ee (72% ee) was measured by chiral HPLC on an OD-H column (^{i}PrOH/hexane 1:99, 0.8 mL/min, λ = 235 nm): Olefin t_r = 43.55, (minor)-enantiomer t_r = 56.90 min and (major)-enantiomer t_r = 62.04 min.

Ethyl 3-(4-Methoxyphenyl)-1H-indole-2-carboxylate (35). After mixing of the initial pale-yellow viscous oil with hexanes and recrystallization of the subsequent pale-yellow solid with ethyl acetate/hexanes a white solid was afforded (58% yield). mp. 109−111 °C (lit. 115−116 °C);[19] R_f = 0.43 (Hexanes/EtOAc, 4:1) after visualization by vanillin; υ_{max} (thin film, cm^{-1}): 2977, 2165, 1655, 1620, 1572, 1503, 1471, 1430, 1387, 1366, 1329, 1307, 1272, 1241, 1199, 1176, 1124, 1035, 949, 907, 876, 848, 839, 811, 774, 755, 745; δ_H (250 MHz, $CDCl_3$): 10.71 (1H, s), 7.55 (2H, dd, *J* 4.0 9.0), 7.35−7.45 (3H, m), 7.08 (1H, t, *J* 8.0), 6.96 (2H, d, *J* 9.0), 4.28 (2H, q, *J* 7.0), 3.89 (3H, s), 1.21 (3H, t, *J* 7.0); δ_C (62.5 MHz, $CDCl_3$): 165.0, 159.2, 133.3, 132.2, 126.3, 125.7, 121.8, 121.1, 120.3, 118.3, 113.4, 109.8, 61.7, 55.6, 14.1; MS *m*/*z* (EI): calcd for $C_{18}H_{17}NO_3$ 295.1208, found 295.1218.

Methyl 4-(4-Methoxyphenyl)-2-oxoquinoline-1(2*H*)-carboxylate (36). Product obtained as an amorphous pale-yellow solid (97% yield). R_f = 0.12 (Hexanes/EtOAc, 4:1); υ_{max} (thin film, cm^{-1}): 3419, 2973, 1777, 1732, 1664, 1608, 1594, 1511, 1492, 1449, 1417, 1374, 1305, 1291, 1267, 1245, 1179, 1132, 1069, 1030, 908, 873, 838, 753; δ_H (250 MHz, $CDCl_3$): 7.59 (1H, dd, *J* 1.5 8.3), 7.59 (1H, t, *J* 6.0), 7.59 (2H, d, *J* 9.0), 7.11−7.23 (2H, m), 6,57 (1H, s), 4.18 (3H, s), 3.89 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 160.3, 159.9, 158.7, 152.9, 136.8, 130.9, 130.1, 128.7, 127.8, 123.2, 120.3, 119.7, 114.4, 114.1, 56.0, 55.4; MS *m*/*z* (EI): calcd for $C_{18}H_{15}NO_4$ 309.1001, found 309.0977.

(−)-Methyl 3,4-Dihydro-4-(4-methoxyphenyl)-2-oxoquinoline-1(2*H*)-carboxylate (37). Product obtained as an amorphous beige solid (80% yield). R_f = 0.18 (Hexanes/EtOAc, 4:1); υ_{max} (thin film, cm^{-1}): 3418, 2975, 1777, 1698, 1663, 1608, 1557, 1511, 1494, 1455, 1436, 1417, 1366, 1305, 1270, 1246, 1179, 1111, 1030, 908, 838, 784, 759; δ_H (250 MHz, $CDCl_3$): 6.98−7.10 (6H, m), 6.85 (2H, d, *J* 9.0), 4.23 (1H, t, *J* 6.8), 4.00 (3H, s), 3.79 (3H, s), 2.95 (2H, d, *J* 6.8); δ_C (62.5 MHz, $CDCl_3$): 168.9, 159.1, 154.2, 136.9, 132.2, 130.4, 129.0, 128.4, 128.0, 125.2, 119.1, 114.6, 55.5, 55.2, 41.2, 40.6; MS *m*/*z* (EI): calcd for $C_{18}H_{17}NO_4$ 311.1158, found 311.1271. The ee (75% ee) was measured by chiral HPLC on an AD column (^{i}PrOH/hexane 1:99 to 10:90 over 19 min then 20:80 over 5 min and hold for a further 11 min at this ratio, 0.8 mL/min, λ = 254 nm): (+)-enantiomer t_r = 26.18 min and (−)-enantiomer t_r = 28.39 min. $[\alpha]_D^{20}$ −13.0 (*c* 1.0, DCM).

(*S*)-3-(3,4-Dichlorophenyl)-2,3-dihydroinden-1-one (38). Product obtained as a white solid (55% yield over 2 steps) following the procedure reported in the literature.[3a] mp. 110−111 °C; R_f = 0.32 (Hexanes/EtOAc, 8:1) after visualization by vanillin; δ_H (250 MHz, $CDCl_3$): 7.82 (1H, d, *J* 7.5), 7.58 (1H, td, *J* 1.3, 7.5), 7.37−7.49 (2H, m), 7.22−7.28 (2H, m), 6.93 (1H, dd, *J* 2.0, 8.3), 4.52 (1H, dd, *J* 3.8, 8.0), 3.18 (1H, dd, *J* 8.3, 19.3), 2.57 (1H, dd, *J* 4.0, 19.3); δ_C (62.5 MHz, $CDCl_3$): 204.9, 156.5, 143.9, 136.7, 135.4, 130.8, 129.7, 128.3, 126.9, 123.5, 46.5, 43.6. NMR data were consistent with the literature values. The ee (89% ee) was measured by chiral HPLC on an OD column (^{i}PrOH/hexane 1:99 to 15:85 over 10 min then hold at this ratio for 6 min, 0.8 mL/min, λ = 254 nm): (*R*)-enantiomer t_r = 11.30 min and (*S*)-enantiomer t_r = 12.15 min. $[\alpha]_D^{20}$ −50.0 (*c* = 1.1, $CHCl_3$)

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Supporting Information Available: General methods, Experimental details, characterization data and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.