Preparation of Tetrasubstituted Olefins Using Mono or Double Aerobic Direct C–H Functionalization Strategies: Importance of Steric Effects

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***Supporting Information

ABSTRACT: A novel protocol for the synthesis of tetrasubstituted olefins through a biomimetic approach has been explored. Both mono- and diarylations were performed under ambient oxygen pressure, giving a range of highly hindered tetrasubstituted alkenes. For diarylation of disubstituted substrates, it was demonstrated that the second arylation is the rate-limiting step of the overall transformation.

INTRODUCTION

Tetrasubstituted olefins constitute an important class of compounds since many of these olefins show significant biological activities (Figure 1). For example, (Z)-Tamoxifen displays effects against breast cancer† while Rofecoxib is a powerful nonsteroidal anti-inflammatory drug.‡ Dibenzoxapin and related compounds have been evaluated as nuclear hormone receptor modulators,§ and finally, tetrasubstituted isocoumberstastatins A-4 have been recently identified as new tubulin inhibitors.†§

Reported efficient methods for accessing such unsaturated structures are mainly based on the use of transition-metal catalysis via carbofunctionalization of alkynes,¶ olefin metathesis,* or cross-coupling reactions.‡ Among the latter, the oxidative Heck coupling has been frequently employed for the preparation of disubstituted alkenes.§ However, only a few examples of successful Heck arylation have been reported regarding the synthesis of tri- or tetrasubstituted olefins.‡b–e There are several problems associated with the oxidative Heck coupling between aromatic heterocycles and trisubstituted olefins to give tetrasubstituted olefins. The problems with the latter reaction can be rationalized by the low reactivity of the trisubstituted substrates. Due to steric hindrance around the unsaturated core, the latter alkenes are not reactive enough to undergo the required cardopalladation. Another problem is associated with the regeneration of the active catalyst. In general, the use of strong oxidants or additives—such as TEMPO (2,2,6,6-tetramethylpiperidine-N-oxyl radical) derivatives or inorganic salts—is required, thus reducing the applicability and sustainability of the reaction. In addition, in the dehydrogenative version of the Heck reaction—the Fujiwara–Moritani reaction—the challenging metal insertion into the aromatic C–H bond makes the synthetic task even more difficult. Therefore, there is a demand for improvements of the synthesis of tetrasubstituted alkenes via the dehydrogenative Heck reaction approach.

In the past few years, we have been involved in the development of new sustainable C–C couplings via C–H activations using a biomimetic approach.¶ Following this concept, the high kinetic barrier preventing the catalyst regeneration is circumvented by the use of catalytic amounts of electron-transfer mediators (ETMs).†‡ In this way, the reduced catalyst can be reoxidized by O2 at atmospheric pressure, producing water as the sole byproduct of the reaction. On the basis of this strategy, we have previously established protocols for the dehydrogenative Heck reaction that have the following advantages: (i) relative low palladium and arene loadings, (ii) utilization of O2 under ambient pressure as the oxidant, and (iii) extension of the scope to nonbiased olefins and heterocycles.

Our continued interest in this field prompted us to explore the preparation of tetrasubstituted olefins via a biomimetic approach, and our contribution is reported herein.

RESULTS AND DISCUSSION

We first planned to prepare a trisubstituted olefin via a dehydrogenative Heck reaction that could be used as starting material for the synthesis of tetrasubstituted olefins. In our previously reported arylation of nonbiased olefins,¶a we showed that acridine as a ligand dramatically enhances the reaction rate and totally controls the site selectivity in the coupling with veratrole. We initiated our studies with a 1:10 ratio of alkene 1a and veratrole (2a) using Pd(OAc)2 (5 mol %) as catalyst, acridine (5 mol %) as ligand, and benzoquinone (BQ) (10 mol %) and iron phthalocyanine Fe(Pc) (2.5 mol %) as electron-transfer mediators in a mixture of acetic acid:dioxane (1:1, v:v)

Received: January 20, 2015
Published: February 5, 2015
Interestingly, we found that formation of the trisubstituted alkene 3aa was accompanied by the tetrasubstituted alkene 4aa. This reaction shows that the biomimetic approach is a viable strategy for providing access to tetrasubstituted olefins. Taking into account that there are not many examples in the literature for the diarylation of alkenes,\textsuperscript{10f,12} it was highly interesting to develop a one-pot double arylation of 1a.

Attempts to increase the rate of the reaction by the use of pure acetic acid as the solvent were unsuccessful and led to only 17\% yield of 4aa (Table 1, entry 2). An increase of the reaction temperature to 100 °C under the standard conditions resulted in an improvement and gave olefin 4aa in a 35\% yield, (Table 1, entry 3). However, a further increase of the reaction temperature to 110 °C decreased the amount of 4aa to 3\% (entry 4). The dramatic decrease of 4aa may be due to decomposition at 110 °C under the acidic conditions. An increase of the catalytic amount of ETMs did not significantly affect the yield of the coupling, and modifications of the solvent ratio led to decreased yields (entries 5–7). We were pleased to find that the use of a higher catalyst loading (entry 8) or an increase of the arene loading (entry 9) improved the yield of 4aa up to 66\%. Considering the importance of the choice of solvent in the Fujiwara–Moritani reaction, we also evaluated the role of a range of cosolvents such as acetonitrile instead of dioxane,\textsuperscript{13} or pivalic acid or propionic acid instead of acetic acid, but none of these changes increased the yield of 4aa (entries 10–12). We chose to conclude our optimization studies with an additional screening of ETMs, but these alternative catalytic systems were not more efficient than those used in the standard conditions (entries 13–14).

The double dehydrogenative sequence for the conversion of disubstituted alkene 1a into trisubstituted alkene 3aa and tetrasubstituted alkene 4aa was monitored by \textsuperscript{1}H NMR spectroscopy (Figure 2). The reaction profile indicates that olefin 1a is almost totally consumed after only 2 h, mostly giving 3aa with only trace amounts of 4aa. Then, the concentration of 3aa is decreasing slowly with concomitant formation of 4aa, demonstrating that the rate-limiting step of the sequence is the formation of the desired tetrasubstituted product. The steric hindrance around the double bond certainly slows down the carbopalladation.
We chose to continue our studies with a range of one-pot diarylations using the optimum conditions (Scheme 1). In most cases, the introduction of directing groups—such as acyl groups—can only be employed to partially control the regio- and the stereoselectivity of tetrasubstituted alkenes. Indeed, simple arenes can potentially undergo metalation at several reactive sites, generating complicated mixtures of isomers after a double cross-coupling. Usually, the site selectivity is controlled by (i) electronic factors with a preference for the most electron-rich carbon, (ii) steric factors with a preference for the less-hindered carbon. First, the influence of the substituents in 1,1-disubstituted alkene substrates was examined by reaction with veratrole 2a as the aromatic coupling partner. We were pleased to find that a range of esters smoothly underwent the diarylation, giving 4aa–4ca in good yields. An acetate and a ketone are both tolerated in the double dehydrogenative cross-coupling, albeit in lower yields (4da and 4ea). An olefin substrate containing an isatin moiety underwent a smooth reaction, resulting in the formation of 4fa in 55% yield. To our satisfaction, the site selectivity of the reaction with 1,2-diethoxybenzene and o-xylene was complete, leading to two highly substituted scaffolds 4ab and 4ac. However, no diarylated product was observed when 1,4-dimethoxybenzene 2d was employed as coupling partner, the reaction yielding only the trisubstituted olefin 3ad in an 83% yield. The second arylation is apparently suppressed due to steric reasons. The lack of reactivity due to steric effects was confirmed by using 1,3-dimethoxybenzene 2e as coupling partner. Indeed, a 63:37 mixture in favor of the ortho-isomer 3ae-α (the most reactive site) was isolated, accompanied by roughly 5% of a diarylated scaffold. In this example, due to its steric hindrance,
3ae-α is already too crowded to perform a second arylation with 2e. In addition, 3ae-β can only react with the β position of 2e, which is unfortunately the less reactive carbon of the arene.

We also confirmed the influence of steric hindrance starting from trisubstituted alkenes 1g and 1h (Scheme 2). Reaction of 1g with arene 2d did not deliver the desired product 5gd, the starting materials being mostly recovered and no identifiable by-product being detected. Furthermore, with arene 2e, only one isomer 5ge was obtained in a 16% yield, whereas 57% of olefin 1g remained intact. These systematic studies on these sterically hindered substrates led to some instructive results: ortho-C–H functionalization of simple arenes is very slow with trisubstituted olefins, illustrating the influence of steric effects on the rate. The reaction was also conducted with 1,3-benzodioxole (1f) as coupling partner, and surprisingly, the selectivity of the coupling was not complete. The desired alkenes 5gf were isolated as a mixture of isomers in a 18:82 ratio in favor of the β-alkenylated scaffold. In light of these results, it was of interest to establish the selectivity of anisole as coupling partner. Anisole is known to mainly undergo palladium insertion at (i) para, (ii) ortho, (iii) meta positions.10a−c As expected, no coupling occurred at the ortho position of anisole, and 5gg was isolated as a mixture of isomers in a 0:46:54 (o:m:p) ratio. Similarly, toluene and chlorobenzene were also successfully employed and only two regioisomers were detected in each case (5gh and 5gi).

Further explore the scope of this transformation, the coupling reaction with 1g (or 1h) was conducted with difunctionalized arenes such as veratrole, naphtalene, or o-xylene, which furnishes a range of densely substituted alkenes 5ga, 5gj, 5gc, and 5ha with synthetically useful yields and complete selectivity.15

**Conclusion**

In summary, we have developed an operationally simple protocol for the synthesis of tetrasubstituted olefins via mono or double aerobic dehydrogenative Heck couplings through a biomimetic approach. It was shown that the steric hindrance around the unsaturated core plays a key role in the selectivity of the reaction, and a range of highly substituted alkenes were isolated with complete chemoselectivity around the double bond and with partial to complete regioselectivity depending on the arene. Remarkably, the reaction involves readily available nonfunctionalized reagents and proceeds at ambient oxygen pressure.

**Experimental Section**

General Information. Reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation and/or spraying with a solution of potassium permanganate, followed by charring at 150 °C. Flash column chromatography was performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm).1H and 13C NMR spectra were recorded on a spectrometer at 400 MHz (13C, 100 MHz). Chemical shifts are given in...
parts per million from tetramethylsilane (TMS) as internal standard. The following abbreviations are used for the proton spectra multiplicities: s: singulet, d: doublet, t: triplet, q: quartet, qh: quintuplet, sextet: sextuplet, m: multiplet. Coupling constants (J) are reported in hertz (Hz). HRMS were recorded using ESI-TOF techniques. Dry solvents were obtained from a VAC solvent purifier. All reagents were obtained from commercial suppliers unless otherwise stated.

Protecting alkenes 1 were prepared following a two-step sequence Baylis–Hillman reaction (giving products 6)/Mitsunobu reaction as described below.

tert-Butyl 2-(Hydroxymethyl)acrylate (6b). The title compound was prepared via Baylis–Hillman reaction according to a literature procedure.18 Experimental data were in accordance with those reported in the previous literature.16 1H NMR (CDCl3, 400 MHz): δ 7.87 (dd, J = 5.6, 3.1 Hz, 2H), 7.45 (dd, J = 5.5, 3.1 Hz, 2H), 4.63 (s, J = 1.5 Hz, 2H), 4.54 (s, J = 1.5 Hz, 2H). 13C NMR (CDCl3, 100 MHz): δ 168.0, 165.9, 142.0, 134.5, 134.3, 132.1, 129.1, 128.8, 126.6, 52.1, 35.9.

2-[(2-Methylene-3-oxobutyl)isoxazoline-1,3-dione (1e). Compound 1e was prepared via a Mitsunobu reaction according to a literature procedure.20 Experimental data were in accordance with those reported in the previous literature.1H NMR (CDCl3, 400 MHz): δ 7.87 (dd, J = 5.5, 3.0 Hz, 2H), 7.45 (dd, J = 5.5, 3.0 Hz, 2H), 4.75 (s, J = 1.5 Hz, 2H). 13C NMR (CDCl3, 100 MHz): δ 180.8, 166.9, 142.0, 134.3, 134.2, 132.7, 132.6, 37.8, 26.0.

Methyl 2-((2,3-Dioxoindolin-1-yl)methyl)acrylate (1f). To a solution of (hydroxymethyl)acrylate 6d (600 mg, 5.17 mmol, 1 equiv) in diethyl ether (25 mL) was added dropwise phosphorus tribromide (53S μl, 5.68 mmol, 1.1 equiv) at 0 °C under argon. After 1 h at 25 °C, NaHCO3 was added and the mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (50 mL) and dried over MgSO4, then filtered and evaporated to yield the desired functionalized olefin. 

Methyl 2-((3-Chlorophenyl)acrylate (1g). Compound 1g was prepared via a Mitsunobu reaction according to a literature procedure.19 Experimental data were in accordance with those reported in the previous literature.16 1H NMR (CDCl3, 400 MHz): δ 7.87 (dd, J = 5.5, 3.0 Hz, 2H), 7.45 (dd, J = 5.5, 3.0 Hz, 2H), 4.63 (s, J = 1.5 Hz, 2H), 4.54 (s, J = 1.5 Hz, 2H). 13C NMR (CDCl3, 100 MHz): δ 168.0, 166.9, 142.0, 134.5, 134.3, 132.1, 129.1, 128.8, 126.6, 52.1, 35.9.

2-((1,3-Dioxoindolin-2-yl)methyl)acrylate (1h). Compound 1h was prepared via a Mitsunobu reaction according to a literature procedure.20 Experimental data were in accordance with those reported in the previous literature.16 1H NMR (CDCl3, 400 MHz): δ 7.90 (s, 1H), 7.81 (dd, J = 7.5, 1.6 Hz, 1H), 7.54 (dd, J = 7.8, 1.4 Hz, 1H), 7.11 (dd, J = 7.5, 0.7 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 6.35 (t, J = 1.3 Hz, 1H), 5.73 (s, J = 1.5 Hz, 1H), 4.58 (s, 1H). 13C NMR (CDCl3, 100 MHz): δ 182.9, 165.9, 158.3, 150.5, 138.6, 133.1, 127.5, 125.5, 124.1, 117.7, 111.1, 52.4, 40.7. HRMS (ESI) m/z: [M + Na]+ calcld for C22H17NaO4, 368.0586, found 368.0589.

(E)-Methyl 2-((1,3-Dioxoindolin-2-yl)ethyl)methylacrylate (1g). Compound 1g was prepared via a Mitsunobu reaction according to a literature procedure.20 Experimental data were in accordance with those reported in the previous literature.16 1H NMR (CDCl3, 400 MHz): δ 7.90 (s, 1H), 7.81 (dd, J = 5.5, 3.1 Hz, 2H), 7.76 (dd, J = 5.5, 3.0 Hz, 2H), 7.46 (d, J = 7.7 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.5 Hz, 1H), 4.75 (s, 2H). 13C NMR (CDCl3, 100 MHz): δ 168.0, 164.7, 143.4, 143.8, 133.9, 133.1, 129.1, 128.8, 126.6, 123.5, 52.1, 35.9.

(E)-Methyl 3-((2-Chlorophenyl)-2-(1,3-dioxoindolin-2-yl)methyl)acrylate (1h). Compound 1h was prepared via a Mitsunobu reaction according to a literature procedure.20 Experimental data were in accordance with those reported in the previous literature.16 1H NMR (CDCl3, 400 MHz): δ 7.90 (s, 1H), 7.81 (dd, J = 5.5, 3.1 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.74 (d, J = 1.1 Hz, 2H), 3.78 (s, 3H). 13C NMR (CDCl3, 100 MHz): δ 168.8, 166.8, 142.0, 134.4, 133.2, 130.4, 128.9, 127.3, 127.3, 53.2, 34.5, 38.8.

General Procedure for the Synthesis of Functionalized Olefins 3, 4, or 5. Pd(OAc)2 (5 mol %), 2,3-dione (260 mg, 1.81 mmol, 1.2 equiv) and K2CO3 (250 mg, 1.81 mmol, 1.2 equiv). The resulting solution was stirred for 20 h at 52 °C. H2O was then added, and the mixture was extracted with ethyl acetate (3 × 30 mL). The organic phase was washed with brine (50 mL) and dried over MgSO4, then filtered and evaporated to yield the desired functionalized olefin.

DOI: 10.1021/acs.joc.5b00148 J. Org. Chem. 2015, 80, 2796–2803
Ethyl 3,3-Bis(3,4-dimethoxyphenyl)-2-((1,3-dioxoisoindolin-2-yl)methyl)acrylate (4aa). Prepared following the general procedure. Compound 4aa was obtained as a red solid in 62% yield (66 mg) after flash chromatography (SiO₂, petroleum ether/ethyl acetate, 7:3 to 5:5). ¹H NMR (CDCl₃, 400 MHz): δ 7.83 (d, J = 5.5, 3.1 Hz, 2H), 7.77 (dd, J = 5.6, 3.1 Hz, 2H), 7.66 (dd, J = 5.5, 3.2 Hz, 2H), 7.14 (d, J = 1.9 Hz, 1H), 7.06 (dd, J = 8.3, 2.0 Hz, 2H), 7.14 (d, J = 1.9 Hz, 1H), 1.71 (d, J = 1.9 Hz, 1H), 6.89 (d, J = 8.2, 2.0 Hz, 1H), 6.84–6.75 (m, 3H), 6.70 (d, 2J = 1.8 Hz, 1H), 4.68 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.79 (s, 2H), 1.09 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 169.0, 168.9, 149.6, 148.9, 143.0, 133.9, 132.1, 127.5, 125.2, 122.7, 112.4, 111.0, 61.1, 56.0, 55.9, 36.0, 14.2. HRMS (ESI) m/z: [M + Na⁺] calcd for C₃₂H₃₃NNaO₈ 548.2184, found 548.2176 (0.8 ppm).

(E)-Ethyl 3-(3,4-Dimethoxyphenyl)-2-((1,3-dioxoisoindolin-2-yl)methyl)acrylate (3aa). Prepared following the general procedure. Compound 3aa was obtained as a red solid in 53% yield (59 mg) after flash chromatography (SiO₂, petroleum ether/ethyl acetate, 7:3 to 6:4). ¹H NMR (CDCl₃, 400 MHz): δ 7.82 (dd, J = 5.5, 3.0 Hz, 2H), 7.70 (dd, J = 5.5, 3.1 Hz, 2H), 7.11 (d, J = 1.9 Hz, 1H), 6.89 (d, J = 8.2, 2.0 Hz, 1H), 6.84–6.75 (m, 3H), 6.70 (d, J = 1.8 Hz, 1H), 4.68 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.79 (s, 2H), 1.09 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 169.7, 167.8, 148.8, 148.6, 148.3, 147.0, 143.8, 133.9, 132.2, 127.3, 121.3, 121.2, 121.7, 112.6, 112.2, 101.8, 81.1, 56.0, 55.9, 55.8, 39.3, 27.4. HRMS (ESI) m/z: [M + Na⁺] calcd for C₃₂H₃₃NNaO₈ 548.2184, found 548.2176 (0.8 ppm).

tert-Butyl 3,3-Bis(3,4-dimethoxyphenyl)-2-((1,3-dioxoisoindolin-2-yl)methyl)acrylate (4ab). Prepared following the general procedure. Compound 4ab was obtained as a red solid in 53% yield (59 mg) after flash chromatography (SiO₂, petroleum ether/ethyl acetate, 7:3 to 5:5). ¹H NMR (CDCl₃, 400 MHz): δ 7.80 (dd, J = 5.5, 3.1 Hz, 2H), 7.67 (dd, J = 5.4, 3.1 Hz, 2H), 6.96 (d, J = 1.7 Hz, 1H), 6.83 (m, 2H), 6.71 (m, 2H), 6.65 (d, J = 1.8 Hz, 1H), 4.67 (s, 2H), 4.10–4.01 (m, 4H), 3.94 (q, J = 7.0 Hz, 2H), 3.85 (q, J = 7.1 Hz, 2H), 1.45–1.34 (m, 12H), 0.83 (t, J = 7.1 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 169.4, 168.0, 149.5, 148.8, 148.7, 148.3, 148.1, 133.9, 132.6, 132.2, 125.0, 123.2, 121.9, 114.9, 114.3, 112.8, 112.5, 64.6, 64.5, 64.3, 60.8, 59.5, 149.9, 149.8, 148.7, 137.9, 134.2, 131.7, 121.3, 121.2, 117.9, 112.3, 112.0, 111.3, 110.5, 65.1, 56.1, 55.9, 55.9, 52.3, 41.2. HRMS (ESI) m/z: [M + Na⁺] calcd for C₃₂H₃₃NNaO₈ 540.1629, found 540.1637 (1.5 ppm).

Ethyl 3,3-Bis(3,4-dimethoxyphenyl)-2-((1,3-dioxoisoindolin-2-yl)methyl)acrylate (4ac). Prepared following the general procedure. Compound 4ac was obtained as a yellow solid in 56% yield (52 mg) after flash chromatography (SiO₂, petroleum ether/ethyl acetate, 6:4). ¹H NMR (CDCl₃, 400 MHz): δ 7.80 (dd, J = 5.5, 3.0 Hz, 2H), 7.66 (d, J = 5.5, 3.0 Hz, 2H), 7.07 (m, 3H), 6.99 (d, J = 7.8 Hz, 1H), 6.96 (s, 1H), 6.89 (d, J = 7.7, 1.9 Hz, 1H), 4.64 (s, 2H), 3.87 (q, J = 7.1 Hz, 2H), 2.21 (s, 3H), 2.17 (s, 3H), 0.81 (t, J = 7.2 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 169.1, 167.9, 149.1, 149.0, 148.9, 148.5, 154.7, 143.0, 132.5, 122.5, 125.3, 123.3, 121.9, 121.8, 112.8, 112.1, 110.9, 110.4, 64.9, 56.1, 55.9, 55.9, 39.3, 30.3, 18.9, 13.6. HRMS (ESI) m/z: [M + Na⁺] calcd for C₃₂H₃₃NNaO₈ 582.2098, found 582.2093 (0.8 ppm).
Prepared following the general procedure. Compound 5ge was obtained as a red solid in 59% yield (52 mg, ratio which could not be assigned and is thus given in no particular order = 0:40:60) after flash chromatography (SiO2, petroleum ether/ethyl acetate/toluene, 5:3:2). 1H NMR (CDCl3, 400 MHz): δ 7.81 (m, 3.16H), 7.69 (m, 3.16H), 7.35–7.11 (m, 14.22H), 4.61 (s, 2H), 4.60 (s, 1.16H), 3.39 (s, 1.74H), 3.38 (s, 3H). 13C NMR (CDCl3, 100 MHz): δ 168.9, 168.9, 167.8, 167.8, 148.9, 148.5, 141.4, 141.2, 140.9, 138.1, 134.5, 134.4, 134.1, 131.2, 131.1, 130.8, 129.9, 129.3, 128.8, 128.6, 128.4, 128.3, 128.2, 127.5, 127.2, 126.4, 123.3, 123.4, 123.2, 52.0, 50.9, 39.0, 39.0. HRMS (ESI) m/z: [M + Na]+ calcd for C27H22ClNNaO6 514.1028, found 514.1035 (0.5 ppm).

(E)-Methyl 3-(3-Chloroacryloyl)-2-(1,3-dioxoisindolin-2-yl)methyl)-3-phenyl Acrylate (5gg). Prepared following the general procedure. Compound 5gg was obtained as a brown solid in 83% yield (50 mg) after flash chromatography (SiO2, petroleum ether/ethyl acetate/ethanol, 7:3). 1H NMR (CDCl3, 400 MHz): δ 7.80 (dd, δ = 5.5, 3.1 Hz, 2H), 7.28 (dd, δ = 5.5, 3.0 Hz, 2H), 7.25 (m, 3H), 7.18 (m, 2.85H), 6.90 (m, 2.85H), 4.68 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.79 (m, 1H), 3.78 (m, 1H), 3.75 (m, 1H), 3.73 (m, 1H), 2.32 (m, 1H), 2.15 (m, 1H), 2.12 (m, 1H), 1.97 (m, 1H), 1.93 (m, 1H). 13C NMR (CDCl3, 100 MHz): δ 169.3, 169.2, 162.9, 161.7, 167.8, 150.2, 142.0, 141.4, 133.9, 133.9, 133.8, 133.7, 133.6, 133.5, 133.4, 133.3, 133.2, 129.6, 129.5, 128.4, 128.3, 128.2, 127.1, 126.8, 126.6, 126.5, 126.3, 125.3, 121.9, 121.8, 121.7, 121.6, 121.5, 121.4, 121.3, 121.2, 121.1, 121.0, 119.8, 108.3, 108.5, 103.1, 103.5, 101.3, 101.2, 50.9, 38.2, 53.7. HRMS (ESI) m/z: [M + Na]+ calcd for C27H22ClNNaO6 514.1015, found 514.1014 (0.5 ppm).

(E)-Methyl 2-((1,3-Dioxoisindolin-2-yl)methyl)-3-(2,4-Dimethoxyphenyl)-2-((1,3-dioxoisindolin-2-yl)methyl)-3-phenyl Acrylate (5ga). Prepared following the general procedure, except that Pd(OAc)2 (7.5 mol %) and acridine (7.5 mol %) were used. Compound 5g was obtained as an inseparable mixture of isomers as a yellow solid in 36% yield (31 mg, ratio which could not be assigned and is thus given in no particular order = 0:46:54) after flash chromatography (SiO2, petroleum ether/ethyl acetate/toluene, 7:3:2). 1H NMR (CDCl3, 400 MHz): δ 7.81 (m, 3.16H), 7.69 (m, 3.16H), 7.35–7.11 (m, 14.22H), 4.61 (s, 2H), 4.60 (s, 1.16H), 3.39 (s, 1.74H), 3.38 (s, 3H). 13C NMR (CDCl3, 100 MHz): δ 168.9, 168.9, 167.8, 167.8, 148.9, 148.5, 141.4, 141.2, 140.9, 138.1, 134.5, 134.4, 134.1, 131.2, 131.1, 130.8, 129.9, 129.3, 128.8, 128.6, 128.4, 128.3, 128.2, 127.5, 127.2, 126.4, 123.3, 123.4, 123.2, 52.0, 50.9, 39.0, 39.0. HRMS (ESI) m/z: [M + Na]+ calcd for C27H22ClNNaO6 514.1015, found 514.1014 (0.5 ppm).

(E)-Methyl 3-(3,4-Dimethoxyphenyl)-2-((1,3-dioxoisindolin-2-yl)methyl)-3-phenyl Acrylate (5gg). Prepared following the general procedure. Compound 5gg was obtained as a brown solid in 83% yield (50 mg) after flash chromatography (SiO2, petroleum ether/ethyl acetate/ethanol, 7:3). 1H NMR (CDCl3, 400 MHz): δ 7.80 (dd, δ = 5.5, 3.1 Hz, 2H), 7.28 (dd, δ = 5.5, 3.0 Hz, 2H), 7.25 (m, 3H), 7.18 (m, 2.85H), 6.90 (m, 2.85H), 4.68 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.79 (m, 1H), 3.78 (m, 1H), 3.75 (m, 1H), 3.73 (m, 1H), 2.32 (m, 1H), 2.15 (m, 1H), 2.12 (m, 1H), 1.97 (m, 1H), 1.93 (m, 1H). 13C NMR (CDCl3, 100 MHz): δ 169.3, 169.2, 161.7, 167.8, 150.2, 142.0, 141.4, 133.9, 133.9, 133.8, 133.7, 133.6, 133.5, 133.4, 133.3, 133.2, 129.6, 129.5, 128.4, 128.3, 128.2, 127.1, 126.8, 126.6, 126.5, 126.3, 125.3, 121.9, 121.8, 121.7, 121.6, 121.5, 121.4, 121.3, 121.2, 121.1, 121.0, 119.8, 108.3, 108.5, 103.1, 103.5, 101.3, 101.2, 50.9, 38.2, 53.7. HRMS (ESI) m/z: [M + Na]+ calcd for C27H22ClNNaO6 514.1015, found 514.1014 (0.5 ppm).
Financial support from the European Research Council (ERC AdG 247014), The Swedish Research Council, and The Knut and Alice Wallenberg Foundation is gratefully acknowledged.

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Notes

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