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Palladium-Catalyzed *Z*-Selective Oxidative Amination of *ortho*-Substituted Primary Anilines with Olefins under an Open Air Atmosphere

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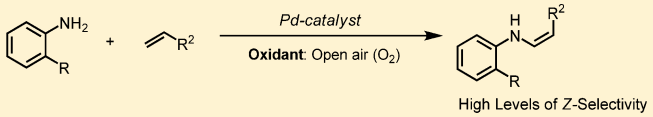
Supporting Information

ABSTRACT: The Pd-catalyzed oxidative amination of olefins with primary anilines has been achieved using molecular dioxygen as the sole oxidant. The use of *ortho*-substituted primary anilines such as *ortho*-toluidine was the key to the successful development of this reaction, providing the corresponding *N*-alkenyl substituted anilines in high yields with unusually high levels of *Z*-selectivity.



Enamine derivatives are an important class of *N*-containing compounds and intermediates for the synthesis of heterocycles and biologically active compounds.[1] For example, *β*-enaminoesters are well-known as starting materials for the syntheses of pyridines,[1a] 1,4-dihydropyridines,[1b,c] pyrazoles,[1d] and furans.[1e]

The transition metal catalyzed oxidative coupling reactions of olefins through sp^2 C−H bond activation represent an important series of reactions in organic chemistry because they allow for a variety of different functional groups to be directly connected to the C═C bond of olefins.[2] The oxidative amination of olefins is an efficient and powerful method for the synthesis of enamine derivatives. In particular, the oxidative amination reaction involving the use of Pd(II) as a catalyst and dioxygen as a reoxidant, which is known as the aza-Wacker type reaction, has recently been the subject of considerable research efforts.[3] For example, Pd and Rh-catalyzed oxidative amination of olefins has been carried out by the use of amides and imides as amination reagents.[4] In addition, White reported the use of Pd and Fe catalysts for the allylic amination of olefins with sulfonamides.[5] These reactions, however, can be limited by their requirement for the use of nonbasic amination reagents in the presence of an external oxidant source such as benzoquinone (BQ), PhBQ, $PhI(OAc)_2$, or $PhI(OPiv)_2$. With this in mind, the development of an oxidative olefin amination method amenable to the use of simple amines using molecular dioxygen as sole oxidant is highly desired.

To date, several methods have been developed for the oxidative amination of olefins using simple amines. Beller[6] reported the oxidative amination of olefins with secondary amines using a rhodium catalyst. In this particular case, however, a variety of byproducts were formed together with the desired oxidative amination products, including the corresponding hydroamination and hydrogenation products of the olefins. We recently reported that Pd(II) catalyzed the oxidative amination reaction of olefins and secondary amines.[7] In this particular transformation, the hydroamination and hydrogenation products of the olefins were not obtained as byproducts. In contrast, for the heterocyclic compounds that were difficult to prepare from the secondary amines, such as quinolines,[8] pyrroles,[9] indoles,[10] dihydropyridines,[11] and pyrazoles,[1d] the enamine derivatives of the corresponding primary amines were important compounds as starting materials for these compounds. The oxidative amination of olefins using primary amines was initially reported in 1981 by Hegedus, with the reactions being conducted in the presence of an excess of reoxidant and salt.[12] The development of an oxidative amination protocol with primary amines using molecular dioxygen as sole oxidant is therefore highly desired.

We recently reported that Pd(II) catalyzes the reaction of olefins and aromatic secondary amines in both an intermolecular aerobic allylic amination[13] and an oxidative C−H olefination of aromatic secondary amines[14] to give (*E*)-allylamines and olefin substituted aromatic amines, respectively, in good yields with levels of high regioselectivity.

In this Note, we report the Pd-catalyzed oxidative amination reaction of olefins and aromatic primary amines in the presence of air and without the need for an external reoxidant, to give the corresponding enamine derivatives in high yields with unusual high levels of *Z*-selectivity. In this reaction, the introduction of substituents at the *ortho* position of the aniline was particularly important, in that the desired products were given in excellent yields only when the anilines were *ortho*-substituted.

To confirm the optimum reaction conditions for this transformation, the reaction of *o*-toluidine with butyl acrylate was selected as a model reaction and conducted under a variety of different reaction conditions. The results for the aerobic oxidative amination are shown in Table 1. The reaction of *o*-toluidine (**1a**, 3 mmol) with butyl acrylate (**2a**, 1 mmol) was performed in the presence of $Pd(OAc)_2$ (0.03 mmol, 3 mol %), and pivalic acid (PivOH, 0.25 mmol) in NMP (0.5 mL) under

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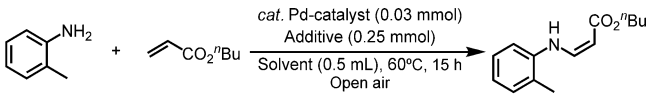
Table 1. Pd-Catalyzed Aerobic Oxidative Amination of *o*-Toluidine (1a) with Butyl Acrylate (2a)[a]



1a 2a 3a

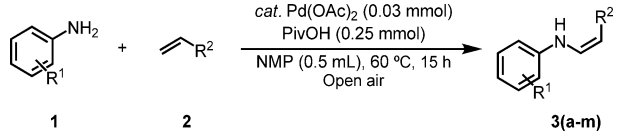
entry	Pd-catalyst	additive	solvent	yield (%)[b,c] 3a
1	$Pd(OAc)_2$	PivOH	NMP	96 (90)
2	none	PivOH	NMP	<1
3	$Pd(OAc)_2$	none	NMP	80
4[d]	$Pd(OAc)_2$	PivOH	NMP	3
5	$Pd(OAc)_2$	PivOH	none	65
6[e]	$Pd(OAc)_2$	PivOH	NMP	79
7	$Pd(OCOCF_3)_2$	PivOH	NMP	88
8	$Pd(acac)_2$	PivOH	NMP	80
9	$PdCl_2$	PivOH	NMP	65
10	$Pd(dba)_2$	PivOH	NMP	92
11	$Pd(OAc)_2$	TMBA	NMP	88
12	$Pd(OAc)_2$	phenol	NMP	85
13	$Pd(OAc)_2$	*p*-TsOH	NMP	3
14	$Pd(OAc)_2$	$AlCl_3$	NMP	4
15	$Pd(OAc)_2$	PivOH	^{t}AmOH	87
16	$Pd(OAc)_2$	PivOH	toluene	72
17	$Pd(OAc)_2$	PivOH	DCE	35

[a]Conditions: **1a** (3 mmol) was allowed to react with **2a** (1 mmol) in the presence of a Pd-catalyst (0.03 mmol) and additive (0.25 mmol) in solvent (0.5 mL) at 60 °C for 15 h under ambient air. [b]GC yields except the value in the parentheses. [c]*E*:*Z* = 1:>20. [d]Reaction was performed under Ar. [e]**1a** (1 mmol) and **2a** (1 mmol) were used. PivOH = pivalic acid. TMBA = 2,4,6-Trimethylbenzoic acid. ^{t}AmOH = 2-Methyl-2-butanol. DCE = 1,2-Dichloroethane.

ambient air at 60 °C for 15 h, giving **3a** in 96% yield (Table 1, entry 1). In the absence of $Pd(OAc)_2$, no reaction occurred, highlighting the importance of the Pd catalyst (Table 1, entry 2). Experimentation also revealed the crucial nature of the PivOH additive for carrying out the aerobic oxidative amination with higher levels of conversion (Table 1, entry 3). Furthermore, when the reaction was conducted under an Ar atmosphere, a low yield of **3a** was observed, indicating the importance of the oxygen in the air (Table 1, entry 4). Under solvent-free conditions, the aerobic oxidative amination product **3a** was obtained in moderate yield (Table 1, entry 5). The best yield was achieved when the reaction of **1a** and **2a** was carried out with a 3:1 ratio (Table 1, entry 1). However, when **1a** and **2a** was carried out to react with 1:1 ratio, the yield of **3a** was still high (Table 1, entry 6). Next, we proceeded to investigate a variety of different Pd-catalysts. When $Pd(OCOCF_3)_2$ was used, the desired product **3a** was obtained in a yield similar to that of $Pd(OAc)_2$ (Table 1, entry 7). The reaction also proceeded in a moderate yield when $PdCl_2$ was used (Table 1, entry 9). It became clear that excellent yields for **3a** were observed when $Pd(dba)_2$ of zerovalent palladium was used as the catalyst (Table 1, entry 10). Our investigation of the additive revealed that 2,4,6-trimethylbenzoic acid (TMBA) and phenol were only moderately beneficial to the reaction (Table 1, entries 11 and 12). When *p*-toluenesulfonic acid (*p*-TsOH) and $AlCl_3$ were added, a significant decrease in the yield of **3a** was observed (Table 1, entries 13 and 14). We found that only pivalic acid had provided a positive improvement to the extent of the reactivity. Polar solvent such as 2-methyl-2-butanol (^{t}AmOH) showed a good trend for this reaction (Table 1, entry 15), whereas the reaction performed poorly in nonpolar and halogen-based solvents to give the desired product **3a** in low yields because they favored the formation of the undesired hydroamination byproduct (Table 1, entries 16 and 17).

To investigate the overall scope of the reaction, a variety of different primary amines and olefins were subjected to the aerobic oxidative amination, under the same conditions as those used for entry 1 in Table 1. The different substrates and associated results are shown in Table 2. The reaction of *o*-

Table 2. Pd-Catalyzed Oxidative Amination of Aniline Derivatives (1) with Olefins (2)[a]



1 2 3(a-m)

entry	R^1	R^2	product	yield (%)[b]
1	*o*-Me (**1a**)	$CO_2{}^n$Bu (**2a**)	**3a**	90
2	*m*-Me (**1b**)	$CO_2{}^n$Bu (**2a**)	**3b**	30
3	*p*-Me (**1c**)	$CO_2{}^n$Bu (**2a**)	**3c**	42
4	*o*-OMe (**1d**)	$CO_2{}^n$Bu (**2a**)	**3d**	71
5[c]	*o*-CF_3 (**1e**)	$CO_2{}^n$Bu (**2a**)	**3e**	56
6	*o*-^{i}Pr (**1f**)	$CO_2{}^n$Bu (**2a**)	**3f**	89
7	2,5-Me_2 (**1g**)	$CO_2{}^n$Bu (**2a**)	**3g**	89
8	H (**1h**)	$CO_2{}^n$Bu (**2a**)	**3h**	38[d]
9	*o*-Me (**1a**)	CO_2Me (**2b**)	**3i**	82
10	*o*-Me (**1a**)	$CO_2{}^t$Bu (**2c**)	**3j**	58
11	*o*-Me (**1a**)	$CO_2{}^n$Cy (**2d**)	**3k**	69
12	*o*-Me (**1a**)	CN (**2e**)	**3l**	40[e]
13	*o*-Me (**1a**)	$CONMe_2$ (**2f**)	**3m**	43

[a]Conditions: Same as those for entry 1, Table 1. [b]*E*:*Z* = 1:>20 unless otherwise noted. [c]Reaction was performed under O_2 (1 atm). [d]*E*:*Z* = 1:4. [e]*E*:*Z* = 7:3.

toluidine (**1a**) with butyl acrylate (**2a**) gave the corresponding product **3a** in 90% yield with high levels of regio- and stereoselectivity (*E*:*Z* = 1:>20) (Table 2, entry 1). *m*- and *p*-Toluidine (**1b** and **1c**) were also used, providing the corresponding product **3b** and **3c** in low yields, but with high levels of regio- and stereoselectivity (*E*:*Z* = 1:>20) (Table 2, entries 2 and 3). Consideration of entries 2 and 3 in Table 2 suggested that the *o*-substituent was important to obtain the desired product in excellent yield. When *o*-anisidine (**1d**) bearing an electron-donating group was used (Table 2, entry 4), the desired product **3d** was obtained in good yield. However, when the electron-withdrawing *o*-trifluoromethylaniline (**1e**) was used (Table 2, entry 5), the desired product **3e** was produced in only moderate yield and required much harsher conditions. The use of the sterically hindered *o*-substituent in *o*-isopropylaniline (**1f**) proved to be a suitable substrate for this reaction (Table 2, entry 6). When the disubstituted aniline 2,5-dimethyl aniline (**1g**) was employed, the desired product was also obtained in excellent yield (Table 2, entry 7). In contrast, when aniline itself (**1h**) was used in the reaction, the desired product (**3h**) was produced in only low yield (Table 2, entry 8). To examine a range of olefins, a variety of different electron-deficient olefins were used in this reaction. When methyl acrylate (**2b**) was used as the coupling partner, the desired product (**3i**) was obtained in good yield (Table 2, entry 9). However, when *tert*-butyl acrylate (**2c**) bearing a

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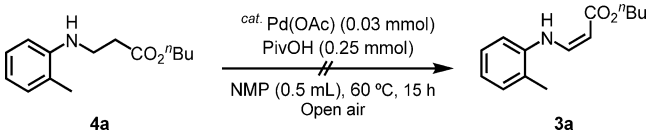
sterically hindered substituent was used, the desired product (**3j**) was produced in only moderate yield (Table 2, entry 10). When acrylonitrile (**2e**) was employed, the desired product was also only obtained in low yield (Table 2, entry 12). In addition, a poor level of stereoselectivity was observed in the desired product (*E*:*Z* = 7:3). The reaction also proceeded using acrylamide (**2f**). The yield of the desired product, however, was low because of deactivation of the Pd-catalyst by the amide group (Table 2, entry 13). Thus, these results indicated that the carbonyl group plays a critical role in generating a high level of stereoselectivity (*E*:*Z* = 1:>20) in the coupling product. Although we found that styrene could also be applied to this oxidative amination reaction with a high level of regioselectivity, the conversion of styrene was low and gave the corresponding coupling product (**3n**) in a relatively lower yield (15%). Under these reaction conditions, the use of phthalimide (as less-basic amide), cyclooctylamine (as more-basic aliphatic amine), and simple alkenes such as 1-octene are totally inactive toward the oxidative amination.

For this transformation, the reaction has the potential to proceed either through the Wacker-type or hydroamination pathways followed by the hydrogenation pathway. To elucidate the reaction pathway, the hydroamination product 3-(*o*-tolylamino)propanoate (**4a**) was synthesized and then examined under the optimized reaction condition with 3-(*o*-tolylamino)propanoate. Analysis revealed that no (*Z*)-butyl 3-(*o*-tolylamino)acrylate (**3a**) was obtained from 3-(*o*-tolylamino)propanoate, indicating that the hydrogenation pathway was not possible within the aerobic oxidative amination process (Scheme 1). In addition, labeling experiment by using aniline-d_7 suggested that the reaction imine−enamine interconversion would be involved during reaction course (Scheme 2).

Scheme 1. Reaction of 3-(*o*-Tolylamino)propanoate (4a) under the Optimized Conditions



4a **3a**

In the current transformation, the *o*-substituents on the aniline derivatives played a critical role in the smooth completion of the reaction. Indeed, when the reaction of aniline (**1h**) and butyl acrylate (**2a**) was performed using a catalyst prepared from $Pd(OAc)_2$ (3 mol % with respect to **2a**) and **1a** (6 mol %) in NMP (0.5 mL) prior to the reaction of **1h** and **2a**, a substantial increase in the yield of **3h** from 38 to 48% was observed. This result suggested that the bulky *o*-methyl substituent of **1a** may have hampered excessive coordination of the aniline nitrogen to the Pd center, likely preventing deactivation of the catalyst through overcoordination (or saturation).

A plausible reaction mechanism for the transformation is shown in Figure 1.[15] The reaction may be initiated by the

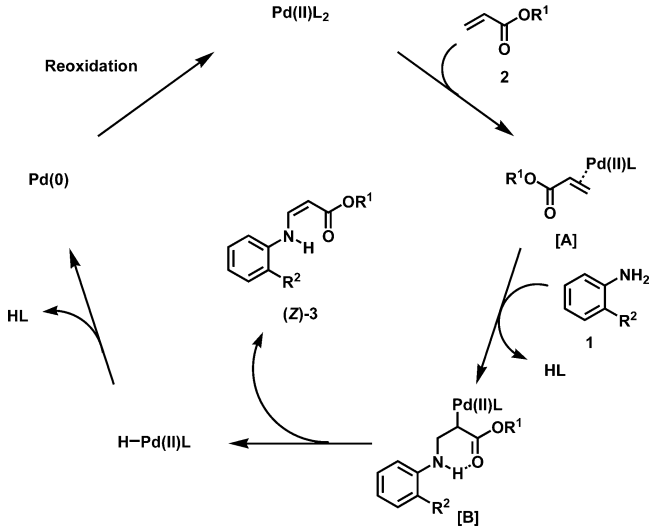


Figure 1. Plausible reaction mechanism for the oxidative amination of *ortho*-substituted amines with olefins.

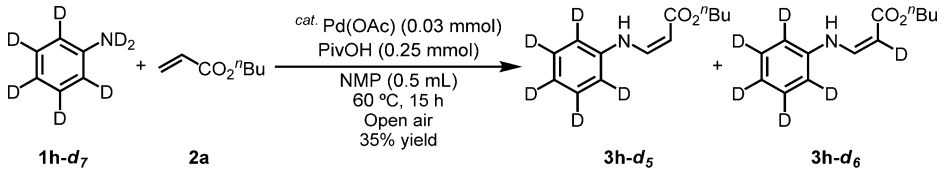
coordination of olefin **2** to Pd(II) leading to palladium(II) complex [**A**]. Nucleophilic attack of the *o*-substituted primary amine to the more electron deficient end of the olefin then occurs to give the six-membered palladium complex [**B**].[16] *β*-Hydride elimination from the six-membered palladium complex [**B**] then occurs, liberating a palladium hydride species to give the amination product (*Z*)-**3**. The palladium hydride species then readily undergoes reductive elimination to give Pd(0), with the resulting Pd(0) being reoxidized by O_2 to Pd(II).

In conclusion, we have demonstrated the aerobic oxidative amination of *o*-substituted primary amines with olefins, which is catalyzed by palladium under mild reaction conditions. The reactions proceeded to give the desired *N*-alkenyl substituted anilines with high levels of regio- and stereoselectivity using primary amines.

EXPERIMENTAL SECTION

General Methods. GLC analysis was performed with a flame ionization detector using a 0.22 mm × 25 m capillary column (BP-5). ^{1}H, ^{13}C, and ^{19}F NMR were measured at 400, 100, and 376 MHz, respectively, in $CDCl_3$ with Me_4Si as the internal standard. The products were characterized by ^{1}H NMR, ^{13}C, and ^{19}F NMR, and GC−MS. The yields of products were estimated from the peak areas based on the internal standard technique using GC. All starting materials were commercially available and used without any purification.

Scheme 2. Oxidative Amination of Aniline-d_7 (1h-d_7) with Butyl Acrylate (2a)



1h-d_7 **2a** **3h-d_5** **3h-d_6**

(**3h-d_5**:**3h-d_6** = 2:3)

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Experimental Procedure. A typical reaction was carried out as follows (Table 1, entry 1). A mixture of butyl acrylate (**2a**) (128 mg, 1 mmol) and *o*-toluidine (**1a**) (322 mg, 3 mmol) was allowed to react with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 3 mol %), pivalic acid (26 mg, 0.25 mmol) in NMP (0.5 mL) at 60 °C for 15 h under open air in a 30 mL round-bottomed flask. The crude reaction mixture was cooled to room temperature. EtOAc (30 mL) was added to the dark solution. The residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1:40) to provide (*Z*)-butyl 3-(*o*-tolylamino)acrylate (**3a**) (210 mg, 90%).

3a. Yield 90% (210 mg), yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (d, J = 12.2 Hz, 1H), 7.28 (dd, J = 12.5, 8.4 Hz, 1H), 7.17−7.14 (m, 2H), 7.00 (d, J = 7.7 Hz, 1H), 6.91 (t, J = 7.7 Hz, 1H), 4.87 (d, J = 8.2 Hz, 1H), 4.13 (t, J = 6.8 Hz, 2H), 2.31 (s, 3H), 1.69−1.62 (m, 2H), 1.43−1.40 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (C═O), 143.1 (CH), 139.0 (C), 130.9 (CH), 127.0 (CH), 125.1 (C), 122.1 (CH), 112.6 (CH), 87.5 (CH), 63.2 (CH_2), 30.8 (CH_2), 19.1 (CH_2), 17.4 (CH_3), 13.7 (CH_3); IR (neat, cm^{-1}) 3308, 2989, 2934, 2874, 1667, 1630, 1603, 1470, 1458, 1300, 1288, 1244, 1202, 1184, 789, 750; GC−MS (EI) m/z (relative intensity) 233 (36) $[M]^+$, 207 (20), 160 (26), 159 (100), 158 (11), 131 (36), 130 (71), 118 (57), 117 (22), 91 (11), 77 (13), 65 (13); HRMS (EI-TOF) m/z calcd for $C_{14}H_{19}NO_2$ $[M]^+$ 233.1416, found 233.1416.

3b. Yield 30% (70 mg), yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (d, J = 12.7 Hz, 1H), 7.23 (dd, J = 12.7, 8.6 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 6.80−6.75 (m, 3H), 4.82 (d, J = 8.2 Hz, 1H), 4.12 (t, J = 6.8 Hz, 2H), 2.31 (s, 3H), 1.69−1.61 (m, 2H), 1.43−1.40 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C═O), 143.0 (CH), 140.6 (C), 139.5 (C), 129.4 (CH), 123.3 (CH), 116.0 (CH), 112.3 (CH), 87.0 (CH), 63.1 (CH_2), 30.9 (CH_2), 21.4 (CH_3), 19.2 (CH_2), 13.7 (CH_3); IR (neat, cm^{-1}) 3374, 2959, 2932, 2872, 1732, 1668, 1627, 1603, 1587, 1495, 1466, 1281, 1250, 1198, 1065, 853, 773, 692; GC−MS (EI) m/z (relative intensity) 233 (93) $[M]^+$, 207 (20), 193 (14), 177 (21), 164 (13), 161 (13), 160 (57), 159 (100), 133 (14), 132 (31), 131 (63), 130 (91), 119 (12), 118 (38), 117 (26), 116 (12), 102 (14), 96 (12), 91 (11), 89 (16), 77 (20), 65 (10), 52 (13), 39 (25), 29 (15), 27 (15); HRMS (EI-TOF) m/z calcd for $C_{14}H_{19}NO_2$ $[M]^+$ 233.1416, found 233.1417.

3c. Yield 42% (98 mg), yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, J = 12.8 Hz, 1H), 7.11 (dd, J = 12.8, 8.2 Hz, 1H), 6.99 (d, J = 8.2 Hz, 2H), 6.75 (d, J = 8.2 Hz, 2H), 4.71 (d, J = 8.2 Hz, 1H), 4.03 (t, J = 6.9 Hz, 2H), 2.19 (s, 3H), 1.59−1.52 (m, 2H), 1.34−1.31 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ170.4 (C═O), 143.3 (CH), 138.2 (C), 131.9 (C), 130.0 (CH), 115.2 (CH), 86.5 (CH), 63.0 (CH_2), 30.9 (CH_2), 20.5 (CH_3), 19.1 (CH_2), 13.7 (CH_3); IR (neat, cm^{-1}) 3308, 3028, 2959, 2872, 1668, 1628, 1584, 1522, 1481, 1292, 1263, 1236, 1194, 810, 789; GC−MS (EI) m/z (relative intensity) 233 (3) $[M]^+$, 160 (13), 159 (100), 158 (25), 131 (28), 130 (67), 103 (11), 77 (15); HRMS (EI-TOF) m/z calcd for $C_{14}H_{19}NO_2$ $[M]^+$ 233.1416, found 233.1417.

3d. Yield 71% (177 mg), yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (d, J = 13.1 Hz, 1H), 7.24 (dd, J = 12.9, 8.4 Hz, 1H), 7.02−6.99 (m, 1H), 6.92−6.86 (m, 3H), 4.86 (d, J = 8.6 Hz, 1H), 4.14 (t, J = 6.8 Hz, 2H), 3.88 (s, 3H), 1.69−1.62 (m, 2H), 1.43−1.39 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ170.0 (C═O), 147.6 (C), 141.6 (CH), 130.1 (C), 121.9 (CH), 120.9 (CH), 111.8 (CH), 110.6 (CH), 87.6 (CH), 63.1 (CH_2), 55.6 (CH_3), 30.8 (CH_2), 19.1 (CH_2), 13.7 (CH_3); IR (neat, cm^{-1}) 3374, 2989, 2872, 1732, 1668, 1628, 1603, 1587, 1495, 1466, 1281, 1250, 1198, 1065, 853, 773, 692; GC−MS (EI) m/z (relative intensity) 249 (100) $[M]^+$, 176 (24), 175 (58), 174 (11), 161 (30), 149 (20), 147 (23), 146 (57), 134 (28), 133 (18), 132 (17), 130 (26), 121 (11), 120 (79), 119 (13), 118 (10), 108 (10), 104 (19), 93 (17), 78 (14), 77 (13), 41 (15), 29 (21), 28 (13); HRMS (EI-TOF) m/z calcd for $C_{14}H_{19}NO_3$ $[M]^+$ 249.1365, found 249.1364.

3e. Yield 56% (161 mg), colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (d, J = 10.9 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.26−7.15 (m, 2H), 7.06 (t, J = 7.7 Hz, 1H), 4.97 (d, J = 8.6 Hz, 1H), 4.16 (t, J = 6.8 Hz, 2H), 1.69−1.62 (m, 2H), 1.43−1.39 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (C═O), 141.9 (CH), 139.0 (C), 133.2 (CH), 126.9 (CH, q, J = 5 Hz), 124.1 (CF_3, q, J = 274 Hz), 121.7 (CH), 117.7 (C, q, J = 30 Hz), 115.3 (CH), 90.7 (CH), 63.6 (CH_2), 30.8 (CH_2), 19.1 (CH_2), 13.7 (CH_3);^{19}F NMR (376 MHz, $CDCl_3$) δ −61.6; IR (neat, cm^{-1}) 3314, 2961, 1674, 1637, 1609, 1517, 1464, 1323, 1285, 1244, 1199, 1165, 1117, 1061, 1036, 793, 756; GC−MS (EI) m/z (relative intensity) 287 (35) $[M]^+$, 269 (15), 232 (11), 231 (25), 214 (33), 213 (100), 194 (40), 187 (13), 186 (11), 185 (14), 172 (23), 166 (22), 165 (49), 146 (24), 145 (13), 41 (17), 29 (17); HRMS (EI-TOF) m/z calcd for $C_{14}H_{16}F_3NO_2$ $[M]^+$ 287.1133, found 287.1131.

3f. Yield 89% (233 mg), light yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (d, J = 12.2 Hz, 1H), 7.26−7.23 (m, 2H), 7.16 (t, J = 7.7 Hz, 1H), 7.01 (t, J = 7.2 Hz, 2H), 4.86 (d, J = 8.6 Hz, 1H), 4.13 (t, J = 6.8 Hz, 2H), 3.19−3.09 (m, 1H), 1.69−1.61 (m, 2H), 1.43−1.40 (m, 2H), 1.29 (d, J = 6.8 Hz, 6H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (C═O), 144.0 (CH), 137.9 (C), 135.9 (C), 126.7 (CH), 125.9 (CH), 122.9 (CH), 114.2 (CH), 87.3 (CH), 63.1 (CH_2), 30.8 (CH_2), 27.6 (CH), 22.5 (CH_3), 19.1 (CH_2), 13.7 (CH_3); IR (neat, cm^{-1}) 3310, 2961, 1665, 1628, 1599, 1499, 1458, 1202, 1188, 789, 750; GC−MS (EI) m/z (relative intensity) 261 (24) $[M]^+$, 209 (14), 207 (40), 147 (20), 146 (100), 145 (11), 144 (42), 131 (12), 43 (12), 41 (18), 32 (30), 29 (12), 28 (16), 17 (40); HRMS (EI-TOF) m/z calcd for $C_{16}H_{23}NO_2$ $[M]^+$261.1729, found 261.1729.

3g. Yield 89% (220 mg), saffron yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (d, J = 12.2 Hz, 1H), 7.27 (dd, J = 12.5, 8.4 Hz, 1H), 7.01 (d, J = 7.7 Hz, 1H), 6.82 (s, 1H), 6.71 (d, J = 7.7 Hz, 1H), 4.85 (d, J = 8.2 Hz, 1H), 4.12 (t, J = 6.8 Hz, 2H),2.29 (s, 3H), 2.26 (s, 3H), 1.68−1.61 (m, 2H), 1.43−1.39 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (C═O), 143.1 (CH), 138.8 (C), 136.7 (C), 130.7 (CH), 122.9 (CH), 122.0 (C), 113.4 (CH), 87.2 (CH), 63.1 (CH_2), 30.8 (CH_2), 21.2 (CH_3), 19.1 (CH_2), 16.9 (CH_3), 13.7 (CH_3); IR (neat, cm^{-1}) 2959, 2934, 1665, 1634, 1597, 1466, 1298, 1279, 1254, 1194, 791; GC−MS (EI) m/z (relative intensity) 247 (85) $[M]^+$, 207 (25), 175 (10), 174 (38), 173 (80), 163 (10), 159 (10), 158 (16), 147 (18), 145 (46), 144 (60), 143 (17), 132 (100), 131 (54), 130 (33), 127 (13), 117 (14), 116 (14), 105 (12), 104 (12), 85 (12), 79 (18), 77 (15), 65 (13), 53 (12), 41 (11), 29 (25), 28 (20), 17 (12); HRMS (EI-TOF) m/z calcd for $C_{15}H_{21}NO_2$ $[M]^+$ 247.1572, found 247.1570.

3h. *E*, *Z* mixture (*E*:*Z* = 1:4) Yield 38% (83 mg), light yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) for the *E*, *Z* mixture, δ 9.88 (d, J = 12.4 Hz, 1H (for the *Z* isomer)), 7.96−7.90 (t, J = 13.2 Hz, 1H (for the *E* isomer)), 7.30−7.21 (m, 5H), 7.15 (d, J = 12.4 Hz, 1H (for the *E* isomer)), 7.00−6.92 (m, 6H), 5.24−5.21 (d, J = 12.8 Hz, 1H (for the *E* isomer)), 4.84 (d, J = 8.8 Hz, 1H (for the *Z* isomer)), 4.13 (t, J = 6.6 Hz, 4H), 1.69−1.58 (m, 4H), 1.46−1.35 (m, 4H), 0.95 (t, J = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) for the *E*, *Z* mixture, δ 170.4 (C═O), 169.1 (C═O), 142.9 (C), 142.8 (C), 140.62 (CH), 140.58 (CH), 129.6 (2CH), 122.4 (CH), 122.3 (CH), 115.4 (CH), 115.2 (CH), 92.4 (CH), 87.3 (CH), 63.4 (CH_2), 63.2 (CH_2), 30.9 (CH_2), 30.8 (CH_2), 19.6 (CH_2), 19.1 (CH_2), 13.71 (CH_3), 13.68 (CH_3); IR (neat, cm^{-1}) 3308, 2959, 2934, 2874, 1668, 1630, 1601, 1587, 1508, 1481, 1449, 1304, 1290, 1238, 1196, 789, 750, 692; GC−MS (EI) for *Z* isomer, m/z (relative intensity) 219 (38) $[M]^+$, 146 (40), 145 (100), 119 (14), 118 (21), 117 (76), 104 (13), 91 (10), 90 (14), 77 (17); HRMS (EI-TOF) for *Z* isomer, m/z calcd for $C_{13}H_{17}NO_2$ $[M]^+$ 219.1259, found 219.1260; GC−MS (EI) for *E* isomer, m/z (relative intensity) 219 (16) $[M]^+$, 162 (47), 118 (100), 92 (32), 77 (13), 15 (8); HRMS (EI-TOF) for *E* isomer, m/z calcd for $C_{13}H_{17}NO_2$ $[M]^+$ 219.1259, found 219.1257.

3i. Yield 82% (157 mg), light yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ10.00 (d, J = 11.8 Hz, 1H), 7.29 (dd, J = 12.5, 8.4 Hz, 1H), 7.18−7.15 (m, 2H), 7.01 (d, J = 7.7 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 4.88 (d, J = 8.2 Hz, 1H), 3.72 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9 (C═O), 143.4 (CH), 139.0 (C), 131.0 (CH), 127.2 (CH), 125.3 (C), 122.3 (CH), 112.8 (CH), 87.1 (CH), 50.7 (CH_3), 17.5 (CH_3); IR (neat, cm^{-1}) 1670, 1630, 1603, 1462, 1300, 1246, 1206, 787, 750; GC−MS (EI) m/z(relative intensity) 191 (68) $[M]^+$, 160 (29), 159 (55), 132 (14), 131 (25), 130 (100), 118 (84),

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117 (30), 91 (22), 77 (17), 65 (23); HRMS (EI-TOF) m/z calcd for $C_{11}H_{13}NO_2$ $[M]^+$ 191.0946, found 191.0945.

3j. Yield 58% (135 mg), white solid: mp 70−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (d, J = 12.2 Hz, 1H), 7.19 (dd, J = 12.2, 8.6 Hz, 1H), 7.14−7.12 (m, 2H), 6.97 (d, J = 7.7 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 4.78 (d, J = 8.6 Hz, 1H), 2.30 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (C═O), 142.3 (CH), 139.3 (C), 130.9 (CH), 127.0 (CH), 125.1 (C), 121.9 (CH), 112.7 (CH), 89.6 (CH), 79.1 (C), 28.4 (CH_3), 17.5 (CH_3); IR (neat, cm^{-1}) 3292, 2984, 1661, 1634, 1603, 1470, 1456, 1391, 1366, 1308, 1288, 1244, 1227, 1167, 1155, 793, 756; GC−MS (EI) m/z (relative intensity) 233 (23) $[M]^+$, 177 (69), 160 (42), 159 (93), 132 (11), 131 (23), 130 (73), 119 (10), 118 (100), 117 (22), 91 (18), 65 (19), 57 (16), 41 (21), 39 (13), 29 (12); HRMS (EI-TOF) m/zcalcd for $C_{14}H_{19}NO_2$ $[M]^+$ 233.1416, found 233.1421.

3k. Yield 69% (179 mg), light yellow solid: mp 50−51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (d, J = 12.2 Hz, 1H), 7.16 (dd, J = 12.5, 8.4 Hz, 1H), 7.06−7.04 (m, 2H), 6.89 (d, J = 7.7 Hz, 1H), 6.80 (t, J = 7.2 Hz, 1H), 4.76 (d, J = 8.2 Hz, 1H), 4.76−4.70 (m, 1H), 2.21 (s, 3H), 1.83−1.81 (m, 2H), 1.66−1.64 (m, 2H), 1.48−1.43 (m, 1H), 1.37−1.29 (m, 4H), 1.20−1.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (C═O), 142.8 (CH), 139.0 (C), 130.8 (CH), 127.0 (CH), 125.0 (C), 122.0 (CH), 112.5 (CH), 88.1 (CH), 71.3 (CH), 31.9 (CH_2), 25.3 (CH_2), 23.9 (CH_2), 17.4 (CH_3); IR (neat, cm^{-1}) 2940, 2862, 1661, 1630, 1603, 1470, 1456, 1306, 1288, 1244, 1209, 1042, 1018, 976, 962, 792, 752, 716; GC−MS (EI) m/z (relative intensity) 259 (43) $[M]^+$, 178 (13), 177 (49), 160 (52), 159 (100), 158 (14), 132 (18), 131 (27), 130 (64), 119 (12), 118 (88), 117 (22), 91 (17), 65 (12), 55 (31), 51 (11), 41 (20), 39 (12), 29 (11), 28 (11); HRMS (EI-TOF) m/z calcd for $C_{16}H_{21}NO_2$ $[M]^+$ 259.1572, found 259.1574.

3l. E, Z mixture (E:Z = 7:3) Yield 40% (63 mg), light brown liquid: ^{1}H NMR (400 MHz, $CDCl_3$) for the E isomer, δ 7.36 (dd, J = 13.6, 11.8 Hz, 1H), 7.23−7.17 (m, 2H), 7.02−6.93 (m, 3H), 4.55 (d, J = 13.6 Hz, 1H), 2.27 (s, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) for the Z isomer, δ7.23−7.17 (m, 3H), 7.02−6.93 (m, 2H), 6.74 (d, J = 12.2 Hz, 1H), 4.23 (d, J = 8.2 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the E, Z mixture, δ 147.4 (CH), 145.5 (CH), 138.0 (C), 137.9 (C), 131.1 (CH), 131.0 (CH), 127.3 (CH), 127.2 (CH), 127.0 (C), 125.4 (C), 123.8 (CH), 123.3 (CH), 121.0 (C), 117.9 (C), 116.9 (CH), 114.8 (CH), 67.9 (CH), 66.3 (CH), 17.4 (CH_3), 17.0 (CH_3); IR (neat, cm^{-1}) 3323, 3069, 2924, 2199, 1645, 1605, 1506, 1474, 1383, 1294, 1051, 966, 748, 712, 604; GC−MS (EI) for the E isomer, m/z (relative intensity) 159 (100) $[M]^+$, 158 (12), 131 (32), 130 (66), 118 (26), 117 (13), 91 (10), 77 (16); HRMS (EI-TOF) for the E isomer, m/z calcd for $C_{10}H_{10}N_2$ $[M]^+$158.0844, found 158.0844; GC−MS (EI) for the Z isomer, m/z (relative intensity) 159 (82) $[M]^+$, 132 (100), 106 (4), 91 (28), 77 (13), 15 (9); HRMS (EI-TOF) for the Z isomer, m/z calcd for $C_{10}H_{10}N_2$ $[M]^+$158.0844, found 158.0846.

3m. Yield 43% (88 mg), yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (d, J = 11.3 Hz, 1H), 7.24 (dd, J = 11.8, 8.6 Hz, 1H), 7.18−7.13 (m, 2H), 7.00 (d, J = 8.2 Hz, 1H), 6.88 (t, J = 7.2 Hz, 1H), 5.05 (d, J = 8.6 Hz, 1H), 3.02 (s, 6H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (C═O), 140.8 (CH), 139.7 (C), 130.8 (CH), 126.9 (CH), 125.1 (C), 121.4 (CH), 112.1 (CH), 86.5 (CH), 37.4 (CH_3), 35.1 (CH_3), 17.7 (CH_3); IR (neat, cm^{-1}) 2928, 1636, 1607, 1576, 1489, 1369, 1285, 1146, 775, 748; GC−MS (EI) m/z (relative intensity) 204 (55) $[M]^+$, 161 (11), 160 (100), 159 (53), 131(21), 130 (50), 117 (16), 91 (10), 77 (12), 65 (11); HRMS (EI-TOF) m/z calcd for $C_{12}H_{16}N_2O$ $[M]^+$ 204.1263, found 204.1261.

3n. E, Z mixture (E:Z = 35:65) Yield 15% (31 mg), yellow solid: mp 149−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$):δ 8.28 (d, 2H), 7.85−7.95 (m, 4H), 7.04−7.49 (m, 17H), 6.86 (d, J = 8.0 Hz, 1H (for the Z isomer)), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) for the E, Z mixture, δ 159.5 (CH), 159.4 (CH), 151.2 (C), 151.1 (C), 136.51 (C), 136.46 (C), 131.8 (CH), 131.2 (CH), 130.4 (CH), 130.2 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 128.32 (CH), 127.12 (CH), 127.10 (CH), 126.70 (CH), 126.69 (CH), 126.4 (C), 126.3 (C), 125.7 (CH), 125.6 (CH), 117.7 (CH), 117.6 (CH), 17.9 (CH_3), 17.8 (CH_3); IR (neat, cm^{-1}) 3323, 3034, 2924, 1518, 1364, 1244, 1211, 1196, 1098, 833, 758; GC−MS (EI) m/z(relative intensity) for Z isomer, 209 (52) $[M]^+$, 194 (100), 132 (13), 106 (1), 103 (4), 91 (42), 77 (8), 27 (3), 15 (1); HRMS (EI-TOF) for Z isomer, m/z calcd for $C_{15}H_{15}N$ $[M]^+$209.1204, found 209.1208; GC−MS (EI) for E isomer, m/z (relative intensity) 209 (6) $[M]^+$, 194 (55), 118 (100), 91 (46), 77 (6); HRMS (EI-TOF) for E isomer, m/z calcd for $C_{15}H_{15}N$ $[M]^+$209.1204, found 209.1203.

Synthesis of 3-(*o*-Tolylamino)propanoate (4a). 3-(*o*-Tolylamino)propanoate (**4a**) was synthesized substrate according the literature procedure.[17] In a 10 mL glass tube were placed butyl acrylate (**2a**) (1281 mg, 10 mmol) and *o*-toluidine (**1a**) (1071 mg, 10 mmol), acetic acid (60 mg, 1.0 mmol), and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity where it was sealed with a pressure lock. The reaction mixture was heated from rt to 200 °C, where it was held by modulating microwave power for a total reaction time of 20 min. Upon completion, the reaction mixture was cooled to room temperature. EtOAc (30 mL) was added to the yellow solution. The residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1:20) to provide butyl 3-(*o*-tolylamino)propanoate (**4a**) (777 mg, 33%).

4a. Yield 33% (777 mg), light yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, J = 7.8 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H), 6.68−6.61 (m, 2H), 4.10 (t, J = 6.6 Hz, 2H), 3.97 (s, 1H), 3.49 (t, J = 6.2 Hz, 2H), 2.64 (t, J = 6.2 Hz, 2H), 2.12 (s, 3H), 1.64−1.57 (m, 2H), 1.39−1.35 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ172.5 (C═O), 145.5 (C), 130.2 (CH), 127.1 (CH), 122.4 (C), 117.1 (CH), 109.6 (CH), 64.5 (CH_2), 39.3 (CH_2), 33.9 (CH_2), 30.6 (CH_2), 19.1 (CH_2), 17.4 (CH_3), 13.6 (CH_3); IR (neat, cm^{-1}) 3429, 2961, 2874, 1732, 1607, 1587, 1516, 1452, 1317, 1256, 1179, 1130, 1061, 746, 716; GC−MS (EI-TOF) m/z (relative intensity) 235 (18) $[M]^+$, 120 (100), 118 (13); HRMS (EI) m/z calcd for $C_{14}H_{21}NO_2$ $[M]^+$ 235.1572, found 235.1572.

Reaction of 3-(*o*-Tolylamino)propanoate (4a) (Scheme 1). A mixture of 3-(*o*-tolylamino)propanoate (**4a**) (235 mg, 1.0 mmol) was allowed to react with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 3 mol %), pivalic acid (26 mg, 0.25 mmol) in NMP (0.5 mL) at 60 °C for 15 h under open air in an 30 mL round-bottomed flask.

Reaction of Aniline-d_7 (1h-d_7) with Butyl Acrylate (2a) (Scheme 2). A mixture of butyl acrylate (**2a**) (128 mg, 1 mmol) and aniline-d_7 (**1h-d_7**) (301 mg, 3 mmol) was allowed to react with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 3 mol %), pivalic acid (26 mg, 0.25 mmol) in NMP (0.5 mL) at 60 °C for 15 h under open air in an 30 mL round-bottomed flask. The crude reaction mixture was cooled to room temperature. EtOAc (30 mL) was added to the dark solution. The residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1:40) to provide (*Z*)-butyl 3-(phenylamino)-acrylate-d_6 and (*Z*)-butyl 3-(phenylamino)acrylate-d_5 (**3h-d_6** and **3h-d_5**, 79 mg, 35%, **3h-d_6**:**3h-d_5** = 3:2).

3h-d_6 and 3h-d_5 Mixture. Yield 35% (79 mg, **3h-d_6**:**3h-d_5**= 3:2), light yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) for the **3h-d_6**, δ 9.89 (d, J = 11.4 Hz, 1H), 7.24 (d, J = 12.4 Hz, 1H), 4.12 (t, J = 6.6 Hz, 2H), 1.69−1.62 (m, 2H), 1.44−1.40 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) for the **3h-d_5**, δ 9.89 (d, J = 11.4 Hz, 1H) 7.24 (dd, J = 12.8, 8.2 Hz, 1H), 4.84 (d, J = 8.2 Hz, 1H),4.12 (t, J = 6.6 Hz, 2H), 1.69−1.62 (m, 2H), 1.44−1.40 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the **3h-d_6**, **3h-d_5** mixture, δ 170.42, 170.39 (2C═O, **3h-d_6** and **3h-d_5**), 142.9, 142.8 (2CH, **3h-d_6** and **3h-d_5**), 140.5 (C), 129.1 (CD), 121.9 (CD), 114.8 (CD), 87.3 (CH), 63.2 (CH_2), 30.9 (CH_2), 19.2 (CH_2), 13.7 (CH_3); IR (neat, cm^{-1}) 3308, 2959, 2934, 2872, 1665, 1626, 1572, 1560, 1391, 1199, 783; GC−MS (EI) for the **3h-d_6**, **3h-d_5** mixture, m/z (relative intensity) 225 (38) $[M]^+$, 224 (39) $[M]^+$, 152 (27), 151 (98), 150 (100), 149 (27), 124 (22), 123 (74), 122 (91), 121 (29), 109 (18), 96 (14), 95 (14), 94 (18), 93 (12), 82 (29), 70 (11); HRMS (EI-TOF) m/z calcd for $C_{13}H_{11}D_6NO_2$ $[M]^+$225.1636, found 225.1633; $C_{13}H_{12}D_5NO_2$ $[M]^+$ 224.1573, found 224.1573.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H, and ^{13}C NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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