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2-Aryl-2-nitroacetates as Central Precursors to Aryl Nitromethanes, α-Ketoesters, and α-Amino Acids

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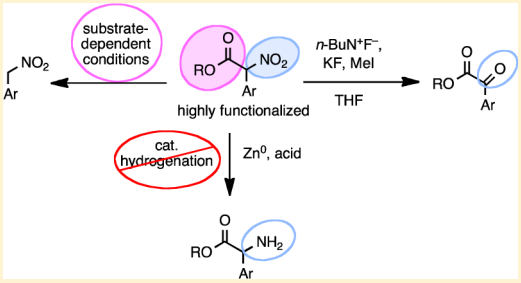
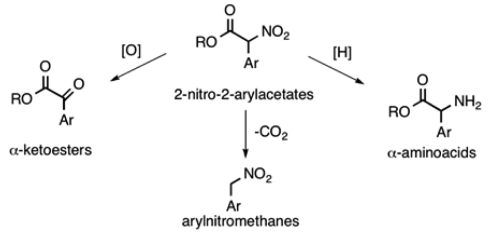
Supporting Information

ABSTRACT: Nitroarylacetates are useful small molecular building blocks that act as precursors to α-ketoesters and aryl nitromethanes as well as α-amino acids. Methods were developed that produce each of these compound types in good yields. Two different conditions for decarboxylation are discussed for substrates with neutral and electron-poor aryl groups versus electron-rich aryl groups. For formation of the α-ketoesters, new mild conditions for the Nef disproportionation were identified.

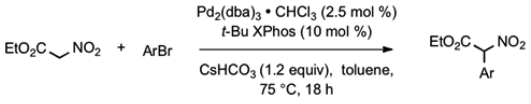


2-Aryl-2-nitroacetates are central precursors (Scheme 1) making them valuable building blocks in synthesis.[1] Access to

Scheme 1. 2-Aryl-2-nitroacetates as Central Precursors



2-aryl-2-nitroacetates[2,3] is best accomplished by our previously reported cross-coupling between nitroacetates and aryl bromides (eq 1).[4] In this paper, we describe efficient methods

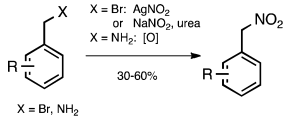


(1)

for the conversion of 2-aryl-2-nitroacetates to several product classes that are surprisingly difficult to make: aryl nitromethanes, α-ketoesters, and α-aryl α-amino acids (Scheme 1).

For aryl nitromethanes, current approaches (Scheme 2), with yields from 30 to 60%, produce multiple byproducts and require arduous purification.[5−7] Low yields are a result of

Scheme 2. Reported Syntheses of Arylnitromethanes



competing benzyl nitrite formation or disproportionation of the phenyl nitromethane product to generate aldehyde. Purification is also difficult as these byproducts coelute with the desired product. Typically excess nitrite reagent is needed, which is also not cost-effective if silver reagents are used. We have recently described another route to aryl nitromethanes that enables the direct coupling of nitromethane with aryl bromides.[8]

Hydrolysis and decarboxylation conditions were initially optimized for the formation of phenylnitromethane and comprised initial treatment with NaOH in EtOH at 80 °C followed by exposure to 1 M HCl in THF after solvent removal (Table 1, entry 1).[9−11] This protocol worked well for substrates with neutral or electron-withdrawing substituents (entries 1−5).

On the other hand, electron-rich substrates were more prone to the Nef reaction (Scheme 3)[12,13] forming an aldehyde byproduct. This observation contradicts Kornblum's report that stabilization of the nitronate anion by an aryl group decelerates the Nef reaction.[14] Apparently, this stabilization is offset by the presence of electron-donating groups on the aromatic ring. To circumvent this problem, less acidic conditions that do not facilitate protonation of the corresponding nitronic acid and that stabilize the nitro group by hydrogen bonding (acetic acid/urea)[14] were employed in the second step for this class of substrates. This procedure slowed the competing elimination of dihydroxyamine [$HN(OH)_2$] and generated aryl nitromethanes in 77−80% yield (Table 1, entries 6−8).

α-Ketoesters are highly valued substrates utilized in a variety of synthetic endeavors.[15−18] Unfortunately, we have found there is no uniform method to generate a broad range of α-ketoesters.[19,20] The reported protocols either utilize harsh acidic conditions or strong oxidizing agents, either of which is incompatible with many desirable functional groups.

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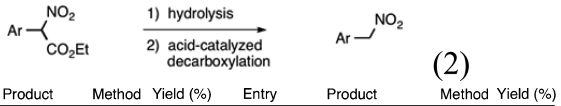
Table 1. Decarboxylation To Form Arylnitromethanes (eq 2)[a]



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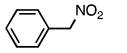
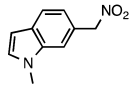
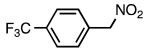
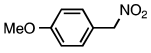
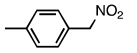
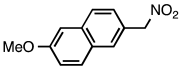
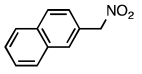
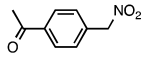
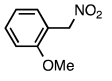
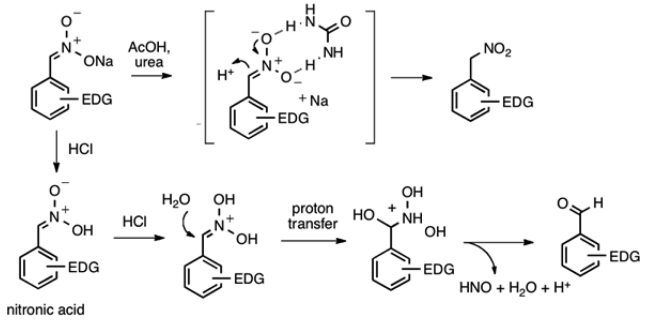
1		A	79	6		B	77
2		A	98	7		B	76
3		A	79	8		B	80
4		A	98				
5		A	76	9		B	88

[a]Reaction conditions. Method A: (1) 1 M NaOH, EtOH (0.14 M), 85 °C, 1 h; (2) 1 M HCl, THF (0.17 M), 85 °C, 1 h. Method B: (1) 1 M NaOH, EtOH/toluene (1:1, 0.14 M), 85 °C, 1 h; (2) urea (17 equiv as a 2.8 M solution in 20% aq AcOH), THF (0.17 M), 0 °C to rt, 1 h.

Scheme 3. Formation of Arylnitromethanes Instead of Aldehyde

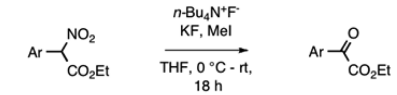


For example, aroylformates are generated by Friedel–Crafts acylation of benzene derivatives using ethyl chlorooxoacetate[21] or by oxidation of the corresponding α-hydroxy-α-arylacetate[22] (Jones reagent) or arylalkynes ($KMnO_4$).[23] In addition, the Friedel–Crafts protocol is restricted to arenes with electron-donating substituents. Alkyl α-ketoesters have been generated by a harsher version of the Nef reaction proceeding via formation of the nitronate salt and subsequent ozonolysis.[24]

Notably, application of conventional Nef conditions[25−28] to the 2-aryl-2-nitroacetates did not provide the expected α-ketoesters. Specifically, deprotonation with aqueous NaOH in THF at rt followed by acidification with 5 M HCl yielded only starting material and some decarboxylated byproduct as a result of ester hydrolysis.[25] An amidine base was also ineffective.[27] Futhermore, exposure of the aryl nitroaceates to 30% H_2O_2 in the presence of aqueous K_2CO_3 in MeOH at rt gave only a 20% conversion by ^1H NMR to the α-ketoester after 24 h.[28]

Significantly, we had observed formation of the α-ketoesters during efforts to α-alkylate the 2-aryl-2-nitroacetates using phase transfer catalysis (PTC) conditions.[29,30] Ultimately, TBAF, MeI, and KF in THF proved quite efficient in generating α-ketoesters. Both electron-poor and electron-rich substrates afforded the α-ketoesters in good yields (Table 2). In many cases, less than 100% isolated yield resulted from a variable amount of an undesired *O*-methylated byproduct.

Table 2. Disproportionation of 2-Aryl-2-nitroacetates (eq 3)[a]



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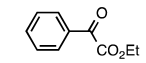
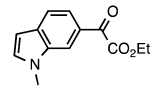
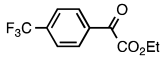
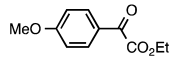
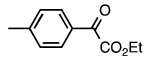
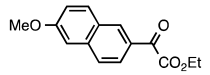
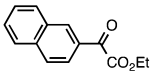
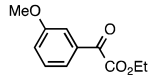
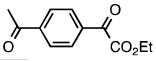
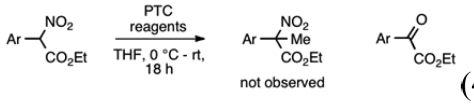
1		72	6		66
2		86	7		80
3		67	8		70
4		74	9		59
5		51			

[a]Reaction conditions: TBAF (5 mol %, 1 M solution in THF), MeI (2.5 equiv), KF (12.5 equiv), THF (0.3 M).

The success of this combination of reagents was unexpected and experiments indicated that all the reagents are important for the transformation (Table 3). The fact that the reactions

Table 3. Exploring Nef Reaction Conditions (eq 4)[a]



entry	reagents	time (h)	conversion[b] (%)
1	TBAF, MeI, KF	1	31
2		2.25	>95
3	TBAF, KF	2	6
4		4	50
5	TBAF	2	6
6	TBAF, MeI	1	1
7		3	>74
8	KF	2	0
9	KF, MeI	2	0
10	TBAH, KF, MeI	2	>95

[a]Reaction conditions: 5 mol % of TBAF (1 M solution in THF), MeI (2.5 equiv), KF (12.5 equiv), THF (0.3M). [b]Determined by ^1H NMR with respect an internal standard (mesitylene).

including MeI were slightly faster than ones that did not (entries 2 vs 3) suggests the involvement of a nitronic ester. Similar compounds have been reported to undergo the Nef reaction.[31] However, the reaction still progresses well without MeI indicating a classical Nef mechanism is concurrently in operation (entry 4). Evidence of a thick precipitate during reaction progression suggests TBAF is necessary to increase anion solubility (entry 9). Without KF (entry 6) the reaction rate is slower, but significant product was observed after 3 h (entry 7). The reaction is sensitive to the amount of water present. Addition of 1 equiv of water aided reaction progress, while 5 equiv inhibited product formation dramatically. Concentrations lower than 0.3 M lead to a slower rate while higher concentrations give an *O*-methylated product with less

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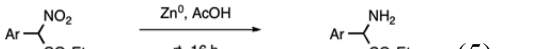
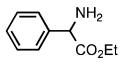
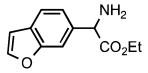
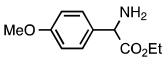
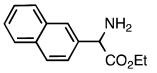
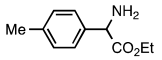
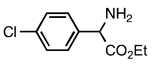
than 10% of the desired product observed. Tetrabutylammonium hydroxide (TBAH) is also sufficient for the transformation (entry 10). However excess water needs to be removed from its solution in water, and it needs to be added as a solution in THF (similar to TBAF). The fluoride anion is suspected to act as a mild base for initial deprotonation of nitroaryl acetate (pK_a = 5.8). Notably, these conditions produced the nitronic ester rather than the aldehyde or ketone for phenylnitromethane or nitrodiphenyl methane.

2-Aryl-2-nitroacetates are also precursors for α-amino acids[32] and arylacetic acids.[33] The generation of unnatural amino acids enables modification of molecular structures in medicinal chemistry.[34,35] For this reason, the synthesis of α-aryl-α-amino acids has been extensively studied.[36−40] 2-Aryl-2-nitroacetates are sensitive to catalytic hydrogenation and usually give poor results.[3] However, reduction of 2-aryl-2-nitroacetates using Zn^0/AcOH (Table 4) proceeds well for electron-rich (entry 2), electron-poor (entry 6), and heteroaromatic (entry 4) substrates.

Table 4. Reduction of 2-Aryl-2-nitroacetates to α-Amino Esters (eq 5)[a]

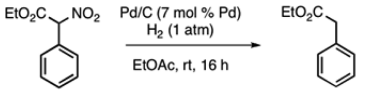


(5)

Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		85	4		63
2		73	5		68
3		71	6		65

[a]Reaction conditions: zinc dust (4 × 6 equiv added in 30 min intervals), AcOH (glacial, 0.2 M).

Reducing catalysts (Table 5), such as Raney nickel in the presence hydrogen (entry 8), also afforded good amounts of the amino ester **3**, but isolated yields were lower than those in Table 4 due to competing cleavage of the benzylic nitro bond to form phenyl acetate **2**.[33] With hydrogen (1 atm), a range of metal catalysts (palladium on carbon, rhodium on alumina, and platinum dioxide) provided mainly the phenyl acetate. Under certain conditions, the phenyl acetate could be produced quantitatively (eq 7). This method serves as an alternative entry



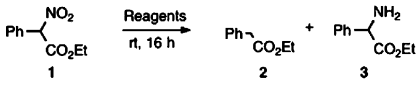
(7)

to aryl acetates relative to the Arndt−Eistert rearrangement[41] of the acid chloride formed from the corresponding benzoic acid, which is not viable on scale due to diazomethane, or a three-step sequence from the benzyl halide involving displacement with cyanide, cyanide hydrolysis, and esterification.[42]

CONCLUSION

In summary, we have developed conditions for selective transformation of 2-aryl-2-nitroacetates to valuable precursors. Decarboxylation afforded aryl nitromethanes, disproportionation produced α-ketoesters, and reduction generated α-amino esters in good isolated yields.

Table 5. Identifying Conditions for Nitro Group Reduction (eq 6)



(6)

entry	reaction conditions	1:2:3[a]
1	$NiCl_2·6H_2O$, $NaBH_4$, MeOH	5:1:0
2	Pt_2O hydrate, H_2 (1 atm), THF	16:3:1
3	Zn^0, HCl, EtOH	1:0:2
4	**Zn^0, AcOH, EtOH**	**0:0:1**
5	Rh/Al_2O_3, H_2 (1 atm), EtOAc	2:1:1
6	Rh/Al_2O_3, H_2 (1 atm), EtOH	0:1:1
7	Raney Nickel, H_2 (1 atm), EtOH	10:1:3
8	Raney Nickel, H_2 (10 atm), EtOH	0:2:7
9	Pd/C, H_2 (1 atm), EtOH	0:1:0
10	**Pd/C, H_2 (1 atm), EtOAc**	**0:1:0**
11	Lindlar's catalyst, H_2 (1 atm), EtOAc	1:0:0
12	Fe^0, AcOH, MeOH	1:0:0

[a]Determined by ^{1}H NMR.

EXPERIMENTAL SECTION

Formation of Aryl Nitromethanes. *Method A.* To a flask was added nitroaryl acetate as a solution in EtOH (0.14 M) followed by an equal volume of 1 M aq NaOH. The mixture was stirred at 85 °C for 1 h at which point the reaction was cooled to rt and the solvents were removed in vacuo. To the remaining salts were added THF (0.17 M with respect to the nitroaryl acetate) and an equal volume of aq HCl (1 M). The mixture was heated at 85 °C for 1 h. The reaction mixture was diluted with EtOAc (1 mL). The layers were separated and the water layer was extracted with EtOAc (3 × 1 mL), dried with $NaSO_4$, and concentrated in vacuo to yield a crude residue. The residue was chromatographed (2:98 to 5:95 EtOAc/hexanes) to afford the desired product.

Method B. To a flask was added nitroaryl acetate as a solution in EtOH/toluene (1:1, 0.14 M) followed by an equal volume of 1 M aq NaOH. The mixture was stirred at 85 °C for 1 h at which point the reaction was cooled to rt and the solvents were removed in vacuo. To the remaining salts were added THF (0.17 M with respect to the nitroaryl acetate) and urea (17 equiv as a 2.8 M solution in 20% aq AcOH) at 0 °C. The mixture was warmed to rt and stirred for 1 h. The reaction mixture was diluted with EtOAc (1 mL). The layers were separated, and the water layer was extracted with EtOAc (3 × 1 mL), dried with $NaSO_4$, and concentrated in vacuo to yield a crude residue. The residue was chromatographed (2:98 to 5:95 EtOAc/hexanes) to afford the desired product.

(Nitromethyl)benzene (Table 1, Entry 1). Method A of the general procedure was carried out on ethyl 2-nitro-2-phenylacetate (25.0 mg, 0.120 mmol). The title compound was obtained as a yellow oil (13.0 mg, 79%). The spectral data were in agreement with reported literature values:[43] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.45 (m, 5H), 5.46 (s, 2H).

1-(Nitromethyl)-4-(trifluoromethyl)benzene (Table 1, Entry 2). Method A of the general procedure was carried out on ethyl 2-nitro-2-(4-(trifluoromethyl)phenyl)acetate (30.0 mg, 0.108 mmol). The title compound was obtained as a yellow oil (21.7 mg, 98%). The spectral data were in agreement with reported literature values:[8] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 5.51 (s, 2H).

1-Methyl-4-(nitromethyl)benzene (Table 1, Entry 3). Method A of the general procedure was carried out on ethyl 2-nitro-2-(*p*-tolyl)acetate (43.7 mg, 0.200 mmol). The title compound was obtained as a yellow oil (24.2 mg, 79%). The spectral data were in agreement with reported literature values:[44] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 5.41 (s, 2H), 2.39 (s, 3H).

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2-(Nitromethyl)naphthalene (Table 1, Entry 4). Method A of the general procedure was carried out on ethyl 2-(naphthalen-2-yl)-2-nitroacetate (21.8 mg, 0.080 mmol). The title compound was obtained as a white solid (15.4 mg, 98%): mp 83−84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94−7.88 (m, 4H), 7.58−7.55 (m, 3H), 5.62 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.9, 133.3, 130.3, 129.3, 128.5, 128.0, 127.5, 127.2, 127.1, 126.7, 80.5; IR (film) 3066, 2927, 2858, 1552, 1367 cm^{-1}; HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{11}H_{10}NO_2$, 188.0712, found 188.0719.

1-(4-(Nitromethyl)phenyl)ethanone (Table 1, Entry 5). Method A of the general procedure was carried out on ethyl 2-(4-acetylphenyl)-2-nitroacetate (28.0 mg, 0.110 mmol). The title compound was obtained as a yellow oil (14.9 mg, 76%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.3 Hz, 2H), 5.52 (s, 2H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 138.3, 134.1, 130.4, 129.1, 79.5, 26.8; IR (film) 3059, 2966, 2927, 2858, 1684, 1552, 1367 cm^{-1}; HRMS-ESI (m/z) [M − H]$^-$ calcd for $C_9H_8NO_3$ 178.0504, found 178.0503.

1-Methyl-5-(nitromethyl)-1H-indole (Table 1, Entry 6). Method B of the general procedure was carried out on ethyl 2-(1-methyl-1*H*-indol-5-yl)-2-nitroacetate (28.5 mg, 0.108 mmol). The title compound was obtained as white solid (15.4 mg, 77%): mp 64−66 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.12 (d, J = 3.1, 1H), 6.53 (d, J = 3.1, 1H), 5.55 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 130.3, 128.8, 123.4, 123.3, 121.0, 109.9, 101.7, 81.1, 33.1; IR (film) 2920, 1552, 1375 cm^1; HRMS-CI (m/z) [M − H]$^-$ calcd for $C_{10}H_9N_2O_2$ 189.0664, found 189.0661.

1-Methoxy-4-(nitromethyl)benzene (Table 1, Entry 7). Method B of the general procedure was carried out on ethyl 2-(4-methoxyphenyl)-2-nitroacetate (30.0 mg, 0.126 mmol). The title compound was obtained as a yellow oil (16.0 mg, 76%). The spectral data were in agreement with reported literature values:[45] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 5.38 (s, 2H), 3.84 (s, 3H).

2-Methoxy-6-(nitromethyl)naphthalene (Table 1, Entry 8). Method B of the general procedure was carried out on ethyl 2-(6-methoxynaphthalen-2-yl)-2-nitroacetate (30.0 mg, 0.100 mmol). The title compound was obtained as a white solid (19.5 mg, 90%): mp 66−71 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.21 (dd, J = 2.1, 8.7 Hz, 1H), 7.17 (d, J = 2.1 Hz, 1H), 5.58 (s, 2H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 135.3, 130.0, 129.8, 128.6, 127.9, 127.2, 124.9, 119.9, 105.8, 80.4, 55.5; IR (film) 2920, 1552, 1375, 1267 cm^{-1}; HRMS-CI (m/z) [M − H]$^-$ calcd for $C_{12}H_{10}NO_3$ 216.0661, found 216.0675.

1-Methoxy-2-(nitromethyl)benzene (Table 1, Entry 9). Method B of the general procedure was carried out on ethyl 2-(2-methoxyphenyl)-2-nitroacetate (46.5 mg, 0.190 mmol). The title compound was obtained as a brown oil (27.9 mg, 88%). The spectral data were in agreement with reported literature values:[46] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (ddd, J = 1.6, 7.5, 7.5 Hz, 1H), 7.31 (dd, J = 1.6, 7.5 Hz, 1H), 7.01 (dd, J = 7.5, 7.5 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 5.49 (s, 2H), 3.86 (s, 3H).

Formation of α-Keto Esters. To a flask under Ar was added nitroaryl acetate as a solution in THF (0.3 M) followed by tetrabutylammonium fluoride (5 mol %, 1 M solution in THF at 0 °C) and KF (12.5 equiv). The reaction mixture was cooled to 0 °C and MeI (2.5 equiv) was added. The mixture was warmed to rt and stirred for 16 h at which point aq HCl (1 mL, 5 M) was added. The aqueous layer was extracted with Et_2O (3 × 2 mL), dried with $NaSO_4$, and concentrated in vacuo to yield a crude residue. The residue was chromatographed (2:98 to 5:95 EtOAc/hexanes) to afford the desired product.

Ethyl 2-oxo-2-phenylacetate (Table 2, Entry 1). The general procedure was employed with ethyl 2-nitro-2-phenylacetate (25.0 mg, 0.120 mmol). The title compound was obtained as a yellow oil (15.5 mg, 72%). The spectral data were in agreement with reported literature values:[47] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, J = 1.1, 8.0 Hz, 2H), 7.67 (td, J = 1.1, 7.8 Hz, 1H), 7.53 (dd, J = 7.8, 7.8 Hz, 2H), 4.47 (q, J = 7.2, 2H), 1.44 (t, J = 7.2 Hz, 3H).

Ethyl 2-Oxo-2-(4-(trifluoromethyl)phenyl)acetate (Table 2, Entry 2). The general procedure was employed with 2-nitro-2-(4-(trifluoromethyl)-phenyl)acetate (30.0 mg, 0.108 mmol). The title compound was obtained as a yellow oil (22.9 mg, 86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 8.3 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H), 4.48 (q, J = 7.1, 2H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1, 162.9, 136.0 (q, J = 33 Hz), 135.4, 130.6, 126.0 (q, J = 3.6 Hz), 123.5 (q, J = 273.1 Hz), 62.9, 14.2; IR (film) 2989, 2943, 1738, 1699, 1174, 1128, 1066, 1012 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{11}H_{10}F_3O_3$ 247.0582, found 247.0575.

Ethyl 2-Oxo-2-(p-tolyl)acetate (Table 2, Entry 3). The general procedure was employed with ethyl 2-nitro-2-(*p*-tolyl)acetate (27.1 mg, 0.120 mmol). The title compound was obtained as a yellow oil (15.4 mg, 67%). The spectral data were in agreement with reported literature values:[47] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 4.45 (q, J = 7.2, 2H), 2.45 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H).

Ethyl 2-(Naphthalen-2-yl)-2-oxoacetate (Table 2, Entry 4). The general procedure was employed with ethyl 2-(naphthalen-2-yl)-2-nitroacetate (21.3 mg, 0.084 mmol). The title compound was obtained as a yellow oil (14.0 mg, 74%). The spectral data were in agreement with reported literature values:[47] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.70−7.57 (m, 2H), 8.10−7.89 (m, 4H), 4.53 (q, J = 7.2 Hz, 2H), 1.48 (t, J = 7.2 Hz, 3H).

Ethyl 2-(4-Acetylphenyl)-2-oxoacetate (Table 2, Entry 5). The general procedure was employed with ethyl 2-(4-acetylphenyl)-2-nitroacetate (28.0 mg, 0.110 mmol). The title compound was obtained as a yellow oil (12.2 mg, 51%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 8.6 Hz, 2H), 8.08 (d, J = 8.6 Hz, 2H), 4.48 (q, J = 7.1, 2H), 2.67 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ197.4, 185.6, 163.2, 141.5, 135.8, 130.5, 128.7, 62.82, 27.1, 14.3; IR (film) 2920, 2966, 1738, 1684, 1197, 1081, 1012 cm^{-1}; HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{12}H_{13}O_4$ 221.0814, found 221.0814.

Ethyl 2-(1-Methyl-1H-indol-5-yl)-2-oxoacetate (Table 2, Entry 6). The general procedure was employed with ethyl 2-(1-methyl-1*H*-indol-5-yl)-2-nitroacetate (29.8 mg, 0.110 mmol). A phosphate buffer (pH = 7) was used instead of aq HCl. The title compound was obtained as a yellow oil (16.8 mg, 66%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 1.6 Hz, 1H), 7.92 (dd, J = 1.6, 8.7 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 3.2 Hz, 1H), 6.64 (d, J = 3.2 Hz, 1H), 4.49 (q, J = 7.1, 2H), 3.84 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.9, 165.2, 140.2, 131.1, 128.2, 126.1, 124.6, 123.0, 109.9, 103.8, 62.1, 33.3, 14.3; IR (film) 2935, 1730, 1668, 1607, 1097, 1020 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{13}H_{13}NO_3Na$ 254.0793, found 254.0793.

Ethyl 2-(4-Methoxyphenyl)-2-oxoacetate (Table 2, Entry 7). The general procedure was employed with ethyl 2-(4-methoxyphenyl)-2-nitroacetate (24.7 mg, 0.103 mmol). The title compound was obtained as a yellow oil (17.7 mg, 80%). The spectral data were in agreement with reported literature values:[47] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 9.0 Hz, 2H), 6.99 (d, J = 9.0 Hz, 2H), 4.44 (q, J = 7.2 Hz, 2H), 3.80 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H).

Ethyl 2-(6-Methoxynaphthalen-2-yl)-2-oxoacetate (Table 2, Entry 8). The general procedure was employed with ethyl 2-(6-methoxynaphthalen-2-yl)-2-nitroacetate (30.0 mg, 0.100 mmol). The title compound was obtained as a yellow oil (18.0 mg, 70%). The spectral data were in agreement with reported literature values:[48] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.03 (dd, J = 8.8 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 4.48 (q, J = 7.1 Hz, 2H), 7.17 (s, 1H), 4.51 (q, J = 7.2 Hz, 2H), 3.97 (s, 3H), 1.47 (t, J = 7.1 Hz, 3H).

Ethyl 2-(3-Methoxyphenyl)-2-oxoacetate (Table 2, Entry 9). The general procedure was employed with ethyl 2-(3-methoxyphenyl)-2-nitroacetate (52.0 mg, 0.220 mmol). The title compound was obtained as a light red oil (26.8 mg, 59%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (ddd, J = 1.5, 1.5, 8.0 Hz, 1H), 7.51 (dd, J = 1.5, 2.5 Hz, 1H), 7.39 (dd, J = 8.0, 8.0 Hz, 1H), 7.19 (ddd, J = 1.5, 2.5, 8.0 Hz, 1H), 4.42 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ186.5, 164.0, 160.1, 133.9, 130.1, 123.3, 122.0,

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113.5, 62.5, 55.7, 14.3; IR (film) 2982, 2839, 1736, 1687, 1192, 1095, 1022, 878, 751, 680 cm^{-1}; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{11}H_{12}O_4Na$ 231.0633, found 231.0651.

Formation of α-Amino Esters. To a flask was added nitroaryl acetate as a solution in glacial AcOH (1 mL). To this solution was added purified zinc dust (4 × 6 equiv in 30 min intervals). The heterogeneous mixture was vigorously stirred for 16 h at rt. At this point, the reaction was quenched with saturated aq K_2CO_3, extracted with EtOAc (3 × 2 mL), dried with $NaSO_4$, and concentrated in vacuo to yield a crude residue. The residue was chromatographed (100% EtOAc) to afford the desired product.

Ethyl 2-Amino-2-phenylacetate (Table 4, Entry 1). The general procedure was employed with ethyl 2-nitro-2-phenylacetate (30.0 mg, 0.140 mmol). The title compound was obtained as a yellow oil (18.0 mg, 85%). The spectral data were in agreement with reported literature values:[49] ^1H NMR (360 MHz, $CDCl_3$) δ 7.42−7.28 (m, 5H), 4.60 (s, 1H) 4.25−4.09 (m, 2H), 2.04 (bs, 2H), 1.21 (t, J = 7.1 Hz, 3H).

Ethyl 2-Amino-2-(4-methoxyphenyl)acetate (Table 4, Entry 2). The general procedure was employed with ethyl 2-(4-methoxyphenyl)-2-nitroacetate (30.0 mg, 0.125 mmol). The title compound was obtained as a yellow oil (19.2 mg, 85%). The spectral data were in agreement with reported literature values:[50] ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.55 (s, 1H) 4.22−4.11 (m, 2H), 3.81 (s, 3H), 2.04 (bs, 2H), 1.21 (t, J = 7.1 Hz, 3H).

Ethyl 2-Amino-2-(p-tolyl)acetate (Table 4, Entry 3). The general procedure was employed with ethyl 2-nitro-2-(*p*-tolyl)acetate (23.6 mg, 0.110 mmol). The title compound was obtained as a yellow oil (15.2 mg, 71%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 4.57 (s, 1H) 4.24−4.10 (m, 2H), 2.38 (s, 3H), 2.03 (bs, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 138.0, 137.2, 129.6, 126.8, 61.5, 58.6, 21.2, 14.2; IR (film) 3383, 3313, 2981, 2927, 2866, 1730, 1097, 1020 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{11}H_{16}NO_2$ 194.1181, found 194.1178.

Ethyl 2-Amino-2-(benzofuran-5-yl)acetate (Table 4, Entry 4). The general procedure was employed with ethyl 2-(benzofuran-5-yl)-2-nitroacetate (22.9 mg, 0.092 mmol). The title compound was obtained as a yellow oily solid (12.7 mg, 63%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 2.1 Hz, 1H), 7.62 (d, J = 1.3 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.32 (dd, J = 1.7, 8.5 Hz, 1H), 6.76 (dd, J = 1.3, 2.1 Hz, 1H), 4.71 (s, 1H), 4.23−4.11 (m, 2H), 2.31 (bs, 2H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 154.5, 145.6, 135.0, 127.7, 123.1, 119.4, 111.5, 106.6, 61.3, 58.7, 14.0; IR (film) 3383, 3313, 2981, 2927, 1730, 1112, 1027 cm^{-1}; HRMS-ESI (m/z) $[M - NH_2]^+$ calcd for $C_{12}H_{11}O_3$ 203.0708, found 203.0718.

Ethyl 2-Amino-2-(naphthalen-2-yl)acetate (Table 4, Entry 5). The general procedure was employed with ethyl 2-(naphthalen-2-yl)-2-nitroacetate (35.1 mg, 0.135 mmol). The title compound was obtained as a yellow oil (21.0 mg, 68%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.85−7.83 (m, 4H), 7.52−7.48 (m, 3H), 4.78 (s, 1H), 4.24−4.13 (m, 2H), 2.11 (bs, 2H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 137.9, 133.5, 133.2, 128.7, 128.1, 127.8, 126.5, 126.3, 125.9, 124.8, 61.6, 59.1, 14.3; IR (film) 3375. 3313, 3059, 2981, 2927, 1730, 1097, 1020 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{14}H_{16}NO_2$ 230.1181, found 230.1185.

Ethyl 2-Amino-2-(4-chlorophenyl)acetate (Table 4, Entry 6). The general procedure was employed with ethyl 2-(4-chlorophenyl)-2-nitroacetate (56.0 mg, 0.230 mmol). The title compound was obtained as a yellow oil (32.2 mg, 65%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.31 (m, 4H), 5.30 (s, 1H), 4.58−4.10 (m, 2H), 2.04 (bs, 2H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 139.0, 134.0, 129.0, 128.4, 61.6, 58.3, 14.2; IR (film) 3383, 2981, 1736, 1178, 1092, 1015, 831, 764 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{10}H_{13}ClNO_2$ 214.0635, found 214.0634.

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR spectroscopic data for all compounds and ^{13}C NMR for all new compounds is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kudyba, I.; Raczko, J.; Juczak, J. *J. Org. Chem.* **2004**, *69*, 2844−2850.
(2) Lehr, F.; Gonnermann, J.; Seebach, D. *Helv. Chem. Acta* **1979**, *62*, 2258−2275.
(3) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1986**, *16*, 133−135.
(4) Metz, A. E.; Berritt, S.; Dreher, S. D.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 760−763.
(5) Ballini, R.; Barboni, L.; Giarlo, G. *J. Org. Chem.* **2004**, *69*, 6907−6908.
(6) Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 1497−1499.
(7) Gianolio, E.; Giovenzana, G. B.; Longo, D.; Longo, I.; Menegotto, I.; Aime, S. *Chem.—Eur. J.* **2007**, *13*, 5785−5797.
(8) Walvoord, R. R.; Berritt, S.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 4086−4089.
(9) Black, A. P.; Babers, F. H. *Org. Synth.* **1939**, *19*, 73−76.
(10) Nayak, M.; Batra, S. *Eur. J. Org. Chem.* **2009**, *21*, 3505−3707.
(11) Grenning, A. J.; Tunge, J. A. *Org. Lett.* **2010**, *12*, 740−742.
(12) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017−1047.
(13) Noland, W. E. *Chem. Rev.* **1955**, *55*, 137−155.
(14) Kornblum, N.; Grahm, G. E. *J. Am. Chem. Soc.* **1951**, *73*, 4041−4043.
(15) Kovács, L. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 471−496.
(16) Cooper, A. J. L.; Ginos, J. Z.; Meister, A. *Chem. Rev.* **1983**, *83*, 321−358.
(17) Wang, F.; Xiong, Y.; Liu, X.; Feng, X. *Adv. Synth. Catal.* **2007**, *349*, 2665−2668.
(18) Li, Z. Z.; Patil, G. S.; Golubski, Z. E.; Hori, H.; Tehrani, K.; Foreman, J. E.; Eveleth, D. D.; Bartus, R. T.; Powers, J. C. *J. Med. Chem.* **1993**, *36*, 3472−3480.
(19) Fennie, M. W.; DiMauro, E. F.; O'Brien, E. M.; Annamalai, V.; Kozlowski, M. C. *Tetrahedron* **2005**, *61*, 6249−6265.
(20) Fennie, M. W., Jr.: Part I: Asymmetric Alkylation of α-Ketoesters and α-Iminoesters using Bifunctional Catalysts; Part II: Strategies for the Synthesis of the Spirocyclic Cores fo the Rubromycins. Ph.D. Thesis, University of Pennsylvania, 2006.
(21) Waldvogel, S. R.; Ianni, A. *Synthesis* **2006**, *13*, 2103−2112.
(22) Lou, J.; Gao, C.; Ma, Y.; Huang, L.; Li, L. *Tetrahedron Lett.* **2006**, *47*, 311−313.
(23) McKillop, A.; Lester, M. S. *Synth. Commun.* **1987**, *17*, 647−656.
(24) Thompson, W. J.; Buhr, C. A. *J. Org. Chem.* **1983**, *48*, 2769.
(25) Santos, R. P.; Lopes, R. S. C.; Lopes, C. C. *Synthesis* **2001**, *6*, 845−848.
(26) Kornilov, V. I.; Glebova, Z. I.; Sudareva, T. P. *Russ. J. Gen. Chem.* **2005**, *75*, 1973−1974.
(27) Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett.* **2002**, *43*, 5233−5235.
(28) Gissot, A.; N'Gouela, S.; Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 8997−9001.
(29) Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931−1934.
(30) Tishkov and co-workers had reported a similar Nef transformation on diphenylnitromethane: Tishkov, A. A.; Schmidhammer,

U.; Roth, S.; Riedle, E.; Mayr, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4623−462.
(31) Kornblum, N.; Brown, R. A. *J. Am. Chem. Soc.* **1965**, *87*, 1742−1747.
(32) González, D. F.; Brand, J. P.; Waser, J. *Chem.—Eur. J.* **2010**, *16*, 9457−9461.
(33) Fessard, T. C.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2078−2081.
(34) Stromgaard, A.; Jensen, A. A.; Stromgaard, K. *Chem. BioChem* **2004**, *5*, 909−916.
(35) Dougherty, D. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 645−652.
(36) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584−4671.
(37) Hong, S.; Lee, J.; Kim, M.; Park, Y.; Park, C.; Kim, M.; Jew, S.; Park, H. *J. Am. Chem. Soc.* **2011**, *133*, 4924−4929.
(38) Kim, S. M.; Lee, J. H.; Kim, D. Y. *Synlett* **2008**, *17*, 2659−2662.
(39) Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 570−576.
(40) Wang, J.; Wang, W.; Li, W.; Hu, X.; Shen, K.; Cheng, T.; Xiaohua, L.; Feng, X. *Chem.—Eur. J.* **2009**, *15*, 11642−11659.
(41) Chiba, J.; Iimura, S.; Yoneda, Y.; Watanabe, T.; Muro, F.; Tsubokawa, M.; Iigou, Y.; Satoh, A.; Takayama, G.; Yokoyama, M.; Takashi, T.; Nakayama, A.; Machinaga, N. *Bioorg. Med. Chem.* **2007**, *15*, 1679−1693.
(42) Leonard, N. J.; Kresge, A. J.; Ōki, M. *J. Am. Chem. Soc.* **1955**, *77*, 5078−5083.
(43) Ando, K.; Shimazu, Y.; Seki, N.; Yamataka, H. *J. Org. Chem.* **2011**, *76*, 3937−3945.
(44) Bug, T.; Lemek, T.; Mayr, H. *J. Org. Chem.* **2004**, *69*, 7565−7576.
(45) Mąkosa, M.; Barbasiewicz, M.; Wojciechowski, K. *Synlett* **2001**, *7*, 1121−1122.
(46) Hauser, F. M.; Baghdanov, V. M. *J. Org. Chem.* **1988**, *53*, 2872−2873.
(47) Meng, Q.; Sun, Y.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Zhang, Z. *J. Org. Chem.* **2008**, *73*, 3842−3847.
(48) Shimada, T.; Kobayashi, Y.; Sago, K. *Tetrahedron: Asymmetry* **2005**, *16*, 3807−3813.
(49) Tanaka, K.; Ootani, M.; Fumio, T. *Tetrahedron: Asymmetry* **1992**, *3*, 709−712.
(50) Sharma, V.; Tepe, J. J. *Org. Lett.* **2005**, *7*, 5091−5094.