JOC The Journal of Organic Chemistry

Article

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Enantioselective Phase-Transfer-Catalyzed Synthesis of Chiral *N*-Substituted 3,3-Dinitroazetidines by Aza-Michael Reaction

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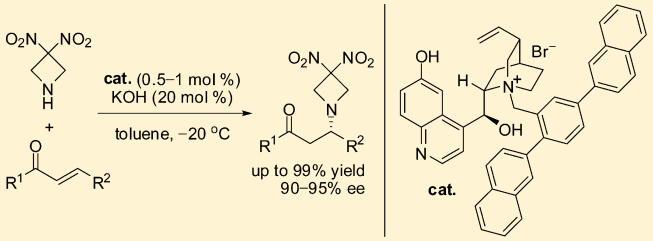
Supporting Information

ABSTRACT: An efficient and highly enantioselective phase-transfer-catalyzed aza-Michael reaction of 3,3-dinitroazetidine, as *N*-centered nucleophile, to α,β-unsaturated ketones has been achieved using a quinidine-based phase-transfer catalyst (0.5−1 mol %), providing chiral *N*-substituted 3,3-dinitroazetidines in good yields (up to 99%) and excellent enantioselectivities (90−95% ee). This is the first example of the use of azetidines as *N*-centered nucleophiles in catalytic enantioselective aza-Michael reactions.



INTRODUCTION

Azetidines are an important class of saturated aza-heterocycles found in naturally occurring organic molecules and pharmaceuticals showing a variety of potent biological activities.[1] For this reason, azetidine synthesis has received considerable attention.[2] In particular, the synthesis of optically pure azetidines has been a subject of active research.[3] However, while catalytic enantioselective synthesis of chiral *C*-substituted azetidines has been widely researched,[4] the corresponding synthesis of chiral *N*-substituted azetidines, which bear a stereogenic carbon center at the α-position of the nitrogen atom, remains unexplored. Despite the significance of the chiral *N*-substituted azetidines as optically pure *N*-heterocyclic pharmacophores in bioactive compounds, the use of azetidines as *N*-centered nucleophiles in catalytic enantioselective aza-Michael reactions[5] has not been reported. Herein, we report the efficient and highly enantioselective phase-transfer-catalyzed[6] aza-Michael reaction of 3,3-dinitroazetidine, as *N*-centered nucleophile, to α,β-unsaturated ketones; to the best of our knowledge, this would be a first example of the use of azetidines as *N*-centered nucleophiles in catalytic enantioselective aza-Michael reactions. The enantioselective phase-transfer-catalyzed aza-Michael reaction affords chiral *N*-substituted 3,3-dinitroazetidines in good yields and excellent enantioselectivities (Figure 1). Because of the inherent energy resulting from the ring strain and high nitrogen content of the 3,3-dinitroazetidine moiety, *N*-substituted 3,3-dinitroazetidines are known as energetic materials.[7] Recently, 1-bromoacetyl-3,3-dinitroazetidine (ABDNAZ), a highly energetic *N*-substituted 3,3-dinitroazetidine, has been developed as a novel class of anticancer agent and is currently in the clinical trial phase.[8] Hence, to explore the scope of application of energetic azetidines as pharmaceutical agents, development of an enantioselective route for the efficient synthesis of chiral *N*-substituted 3,3-dinitroazetidines is highly desirable.

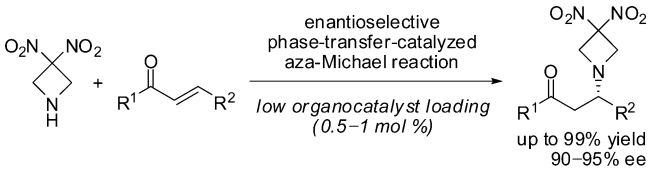


Figure 1. Enantioselective phase-transfer-catalyzed aza-Michael reaction of 3,3-dinitroazetidine to α,β-unsaturated ketones.

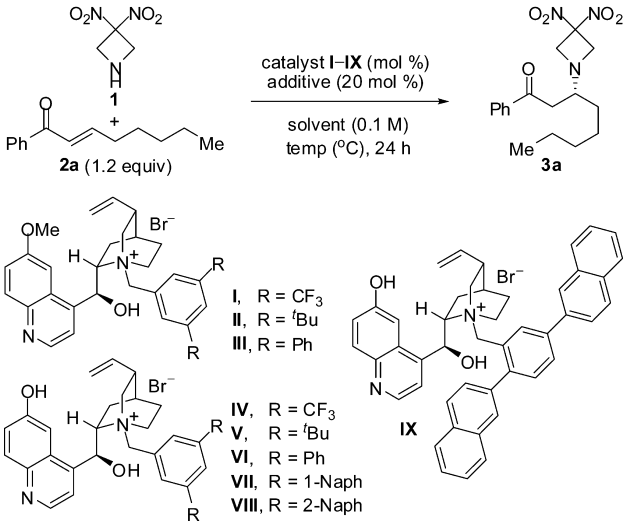
RESULTS AND DISCUSSION

To explore the feasibility of the phase-transfer-catalyzed enantioselective synthesis of chiral *N*-substituted 3,3-dinitroazetidines by aza-Michael reaction, a series of reactions between 3,3-dinitroazetidine (**1**) and (*E*)-1-phenyloct-2-en-1-one (**2a**), using potassium hydroxide (20 mol %) as the base additive, was performed in toluene at ambient temperature, in the presence of quinidine-based phase-transfer catalysts **I**−**III**. Reactions with these catalysts afforded the corresponding aza-Michael product **3a** in good to excellent yields but with very low enantioselectivities (Table 1, entries 1−3). However, when using chiral phase-transfer catalyst **IV**, which has a hydroxyl group instead of the methoxy group in the quinoline moiety, the phase-transfer reaction furnished the desired product **3a** in 74% yield, with a considerably increased ee of 55% (Table 1, entry 4). Therefore, further reactions using other chiral phase-transfer catalysts **V**−**IX**, having a hydroxyl group, were carried out under otherwise identical conditions (Table 1, entries 5−9). Among these catalysts, **IX** proved to be the best, affording the corresponding product **3a** in 91% yield and 84% ee. Varying the solvent revealed that toluene was ideal for the phase-transfer reaction (Table 1, entries 10−12 vs entry 9). In addition, among the base additives tested, potassium hydroxide

Received: September 10, 2015
Published: October 27, 2015

DOI: 10.1021/acs.joc.5b02124
J. Org. Chem. 2015, 80, 11435−11440

Table 1. Optimization of Enantioselective Phase-Transfer-Catalyzed Aza-Michael Reactions of 3,3-Dinitroazetidine (1) to (*E*)-1-Phenyloct-2-en-1-one (2a)[a]



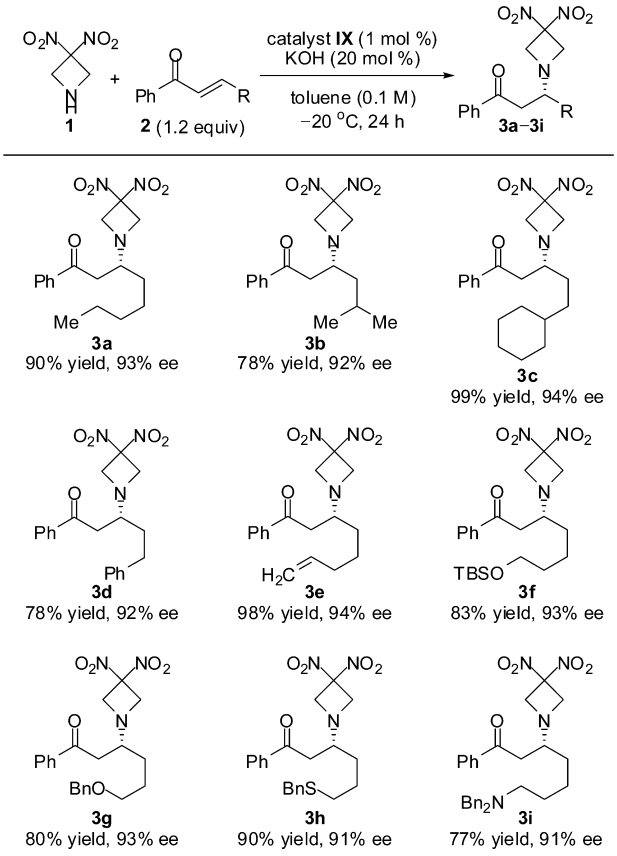
entry	catalyst (mol %)	solvent	additive	temp (°C)	yield[b] (%)	ee[c] (%)
1	**I** (10)	toluene	KOH	rt	88	2
2	**II** (10)	toluene	KOH	rt	99	2
3	**III** (10)	toluene	KOH	rt	67	1
4	**IV** (10)	toluene	KOH	rt	74	55
5	**V** (10)	toluene	KOH	rt	94	69
6	**VI** (10)	toluene	KOH	rt	83	80
7	**VII** (10)	toluene	KOH	rt	85	41
8	**VIII** (10)	toluene	KOH	rt	94	80
9	**IX** (10)	toluene	KOH	rt	91	84
10	**IX** (10)	CH_2Cl_2	KOH	rt	73	61
11	**IX** (10)	$CHCl_3$	KOH	rt	72	69
12	**IX** (10)	THF	KOH	rt	77	2
13	**IX** (10)	toluene	NaOH	rt	92	78
14	**IX** (10)	toluene	Na_2CO_3	rt	57	8
15	**IX** (10)	toluene	K_2CO_3	rt	93	80
16	**IX** (10)	toluene	KOH	0	96	88
17	**IX** (10)	toluene	KOH	−10	96	90
18	**IX** (10)	toluene	KOH	−20	93	93
19	**IX** (5)	toluene	KOH	−20	93	93
20	**IX** (2)	toluene	KOH	−20	90	93
21	**IX** (1)	toluene	KOH	−20	90	93

[a]Procedure: **2a** (0.24 mmol) was added to a mixture of **1** (0.2 mmol), catalyst (0.02, 0.01, 0.004, or 0.002 mmol), and additive (0.04 mmol) in the solvent (2 mL) in one portion. The mixture was stirred at room temperature (rt), 0, −10, or −20 °C for 24 h. The solvent was removed, and the residue was isolated by silica gel chromatography. [b]Isolated yield. [c]Determined by chiral HPLC analysis (Chiralpak AD-H).

was ideal for the reaction (Table 1, entries 13−15 vs entry 9). Lowering the reaction temperature to −20 °C provided **3a** in 93% yield, with an increased ee of 93% (Table 1, entries 16−18). Finally, reducing the catalyst loading capacity to 1 mol % produced **3a** in 90% yield, while the ee of 93% was sustained (Table 1, entries 19−21).

Subsequently, the scope of α,β-unsaturated ketones as substrates in the enantioselective phase-transfer-catalyzed aza-Michael reaction of 3,3-dinitroazetidine (**1**) was explored under the optimized conditions (Schemes 1 and 2). The reactions of

Scheme 1. Enantioselective Phase-Transfer-Catalyzed Aza-Michael Reactions of 1 to Various 3-Substituted (*E*)-1-Phenylprop-2-en-1-ones 2[a]



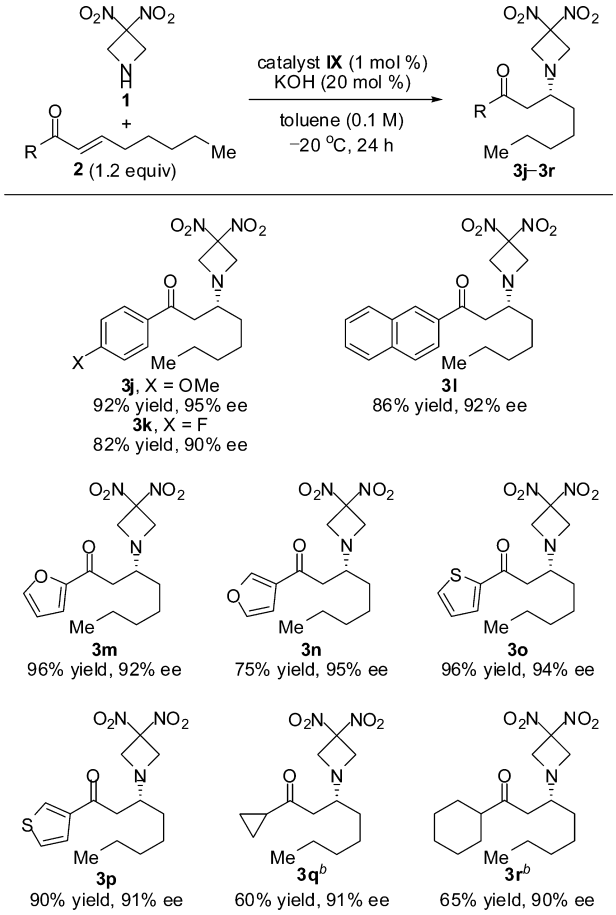
[a]Procedure: **2** (0.24 mmol) was added to a mixture of **1** (0.2 mmol), catalyst **IX** (0.002 mmol), and KOH (0.04 mmol) in toluene (2 mL) in one portion. The mixture was stirred at −20 °C for 24 h. The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H or Chiralpak AD-H).

1 with an assortment of 3-substituted (*E*)-1-phenylprop-2-en-1-ones **2** bearing alkyl, substituted alkyl, protected hydroxyalkyl, benzyl-protected mercaptoalkyl, and dibenzyl-protected aminoalkyl substituents gave the corresponding aza-Michael products **3a−3i** in good yields and excellent enantioselectivities (Scheme 1). Enantioselective phase-transfer-catalyzed aza-Michael reactions of 3,3- dinitroazetidine (**1**) were then explored with a series of 1-substituted (*E*)-oct-2-en-1-ones **2** bearing electron-rich aryl, electron-deficient aryl, aryl, heteroaryl, and cycloalkyl substituents (Scheme 2). In all cases, the desired aza-Michael products **3j−3r** were obtained in good yields and excellent enantioselectivities.

To further investigate the catalyst loading capacity, phase-transfer reactions of **1** were carried out with α,β-unsaturated ketones **2**, in the presence of 0.5 mol % of catalyst **IX** under otherwise identical conditions; the desired products **3a** and **3m** were obtained in good yields and excellent enantioselectivities. The results were comparable to those of the same reactions performed using 1 mol % of catalyst **IX** (**3a** in Scheme 3 vs Scheme 1; **3m** in Scheme 3 vs Scheme 2). Under the favorable conditions with a low catalyst loading of 0.5 mol %, the aza-Michael product **3s** was obtained in 82% yield and 91% ee (Scheme 3). The absolute stereochemical assignments of all the aza-Michael products were made on the basis of the single-

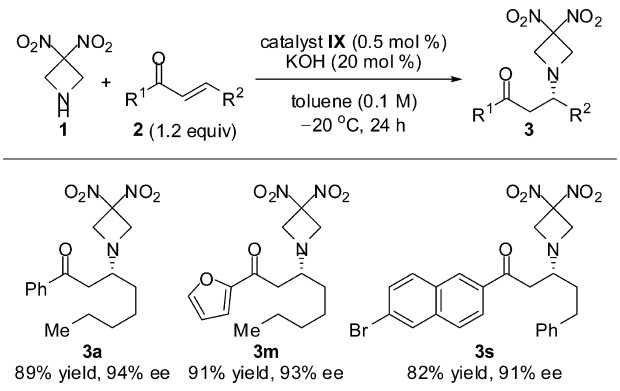
DOI: 10.1021/acs.joc.5b02124
J. Org. Chem. 2015, 80, 11435−11440

Scheme 2. Enantioselective Phase-Transfer-Catalyzed Aza-Michael Reactions of 1 to Various 1-Substituted (*E*)-Oct-2-en-1-ones 2[a]



[a]Procedure: **2** (0.24 mmol) was added to a mixture of **1** (0.2 mmol), catalyst **IX** (0.002 mmol), and KOH (0.04 mmol) in toluene (2 mL) in one portion. The mixture was stirred at −20 °C for 24 or 72 h. The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H). [b]For 72 h.

Scheme 3. Enantioselective Phase-Transfer-Catalyzed Aza-Michael Reactions of 1 to α,β-Unsaturated Ketones 2 with Low Catalyst Loading[a]



[a]Procedure: **2** (1.2 mmol) was added to a mixture of **1** (1 mmol), catalyst **IX** (0.005 mmol), and KOH (0.2 mmol) in toluene (10 mL) in one portion. The mixture was stirred at −20 °C for 24 h. The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H).

crystal X-ray diffraction analysis of the oxime derivative **4**, which was generated from **3s**, as described in the Supporting Information.

The proposed transition state of the aza-Michael reaction is depicted in Figure 2, on the basis of the absolute stereochemistry of the aza-Michael products. The substrate is presumably captured by the catalyst via hydrogen bonding between the carbonyl oxygen of the substrate and the chiral secondary hydroxyl group of the catalyst. The anionic 3,3-dinitroazetidine nucleophile, which is generated by deprotonation of 3,3-dinitroazetidine by the base additive, would interact with the ammonium cation of the catalyst via ion pairing. In addition, the oxygen atom of the nitro group in the azetidine nucleophile would form a hydrogen bond with the free hydroxyl group of the quinoline moiety in the catalyst. Thus, the anionic 3,3-dinitroazetidine nucleophile would be optimally positioned between the catalyst and the substrate. Therefore, aza-Michael reaction of the anionic azetidine nucleophile occurs from the Re face of the substrate and provides the desired product.

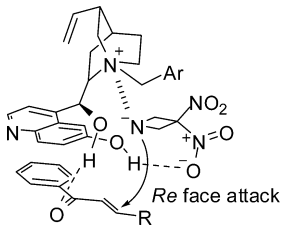


Figure 2. Proposed transition state of the aza-Michael reaction.

CONCLUSION

In conclusion, an efficient and highly enantioselective phase-transfer-catalyzed aza-Michael reaction of 3,3-dinitroazetidine, as the *N*-centered nucleophile, to α,β-unsaturated ketones has been achieved using a quinidine-based phase-transfer catalyst **IX** (0.5−1 mol %) and potassium hydroxide as the base additive. The phase-transfer reaction affords chiral *N*-substituted 3,3-dinitroazetidines in good yields (up to 99%) and excellent enantioselectivities (90−95% ee). To the best of our knowledge, this is the only example of the use of azetidines as *N*-centered nucleophiles in catalytic enantioselective aza-Michael reactions. This strategy provides an efficient route for the enantioselective synthesis of a variety of chiral *N*-substituted 3,3-dinitroazetidines, which may serve as potential core structures for biologically active compounds. The application of these species to the synthesis of bioactive compounds will be a topic of further research.

EXPERIMENTAL SECTION

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer with tetramethylsilane as the internal reference. HRMS data were measured on a magnetic sector−electric sector double focusing mass analyzer with FAB ionization source. Enantiomeric excess values were determined by HPLC analysis with chiral stationary phase column. 3,3-Dinitroazetidine (**1**)[9] and α,β-unsaturated ketones **2**[10] were prepared according to the reported procedures.

Preparation of Catalysts I−IX. Catalysts **I**−**VIII** were prepared according to the reported procedures.[11]

*1-[2,5-Di(naphthalen-2-yl)benzyl]-2-[(S)-hydroxy(6-hydroxyquinolin-4-yl)methyl]-5-vinyl-1-azoniabicyclo[2.2.2]octane Bromide (catalyst **IX**).* 2,2′-[2-(Bromomethyl)-1,4-phenylene]dinaphthalene

DOI: 10.1021/acs.joc.5b02124
J. Org. Chem. 2015, 80, 11435−11440

(1.4 g, 3.3 mmol) was added to a solution of 4-[(1*S*)-hydroxy(8-vinylquinuclidin-2-yl)methyl]quinolin-6-ol[12] (0.93 g, 3 mmol) in THF (15 mL, 0.2 M) at rt, and then the mixture was allowed to stir at reflux. After 12 h, the mixture was cooled to rt. The solvent was removed, and the residue was purified by flash column chromatography (SiO_2, 5% MeOH in EtOAc) to provide the catalyst **IX** in 64% yield (1.41 g, 1.92 mmol) as a white solid: mp 209−210 °C; $[\alpha]_D^{23}$ +172.4 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (br s, 1H), 8.92 (s, 1H), 8.50 (d, *J* = 4.5 Hz, 1H), 8.26 (br s, 1H), 8.12 (s, 2H), 7.99 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.67−7.49 (m, 6H), 7.45−7.35 (m, 5H), 7.22−7.19 (m, 2H), 7.16−7.14 (m, 1H), 6.57−6.52 (m, 2H), 6.14 (d, *J* = 12.5 Hz, 1H), 5.81 (d, *J* = 13.0 Hz, 1H), 5.23−5.17 (m, 1H), 4.82 (s, 1H), 4.70 (d, *J* = 10.5 Hz, 1H), 4.50 (s, 1H), 4.24−4.18 (m, 2H), 2.92−2.87 (m, 1H), 2.81−2.77 (m, 1H), 2.65−2.59 (m, 1H), 2.42 (s, 1H), 1.92−1.87 (m, 1H), 1.62−1.52 (m, 2H), 1.43−1.39 (m, 1H), 0.52−0.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 146.4, 143.4, 142.4, 141.8, 139.5, 136.8, 135.3, 134.8, 134.4, 133.2, 132.5, 132.5, 132.1, 130.8, 128.8, 128.5, 128.4, 128.3, 128.2, 128.2, 127.4, 127.2, 127.0, 126.1, 126.1, 125.7, 125.7, 125.6, 124.6, 124.3, 120.9, 118.9, 116.5, 104.4, 66.6, 66.0, 58.0, 55.8, 54.5, 36.6, 26.2, 23.4, 21.2; FTIR (neat) 3144, 3050, 1728, 1618, 1498, 1461, 1393, 1219, 1130, 925, 814, 747 cm^{-1}; HRMS (FAB) calcd for $[M - Br]^+$ $C_{46}H_{41}N_2O_2$ 653.3168, found 653.3170.

Typical Procedure for the Enantioselective Phase-Transfer-Catalyzed Aza-Michael Reactions of 3,3-Dinitroazetidine to α,β-Unsaturated Ketones. α,β-Unsaturated ketone **2** (0.24 mmol) was added to a mixture of 3,3-dinitroazetidine (**1**) (0.2 mmol), catalyst **IX** (0.002 mmol), and KOH (0.04 mmol) in toluene (2 mL) in one portion. The mixture was stirred at −20 °C for 24 or 72 h. The solvent was removed, and the residue was purified by flash column chromatography (SiO_2, 10% EtOAc in hexanes) to provide the corresponding products **3**.

Typical Procedure for the Enantioselective Phase-Transfer-Catalyzed Aza-Michael Reactions of 3,3-Dinitroazetidine to α,β-Unsaturated Ketones with Low Catalyst Loading. α,β-Unsaturated ketone **2** (1.2 mmol) was added to a mixture of 3,3-dinitroazetidine (**1**) (1 mmol), catalyst **IX** (0.005 mmol), and KOH (0.2 mmol) in toluene (10 mL) in one portion. The mixture was stirred at −20 °C for 24 h. The solvent was removed, and the residue was purified by flash column chromatography (SiO_2, 10% EtOAc in hexanes) to afford the corresponding products **3**.

*(R)-3-(3,3-Dinitroazetidin-1-yl)-1-phenyloctan-1-one (**3a**).* Yellow oil (63 mg, 90%); $[\alpha]_D^{22}$ −32.3 (*c* 1, $CHCl_3$, 93% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95−7.93 (m, 2H), 7.61−7.58 (m, 1H), 7.50−7.47 (m, 2H), 4.15−4.06 (m, 4H), 3.29−3.24 (m, 1H), 3.09−2.96 (m, 2H), 1.51−1.45 (m, 1H), 1.40−1.34 (m, 1H), 1.33−1.21 (m, 6H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 136.6, 133.4, 128.7, 127.9, 107.5, 60.6, 59.8, 40.2, 31.8, 31.3, 24.4, 22.4, 13.8; FTIR (neat) 2930, 2860, 1683, 1565, 1448, 1371, 1329, 1210, 990, 754, 689 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{17}H_{24}N_3O_5$ 350.1716, found 350.1719; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 254 nm) t_R = 12.1 min (major isomer), 15.4 min (minor isomer).

*(R)-3-(3,3-Dinitroazetidin-1-yl)-5-methyl-1-phenylhexan-1-one (**3b**).* Yellow oil (52 mg, 78%); $[\alpha]_D^{23}$ −37.1 (*c* 1, $CHCl_3$, 92% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95−7.94 (m, 2H), 7.62−7.59 (m, 1H), 7.51−7.47 (m, 2H), 4.16−4.03 (m, 4H), 3.37−3.32 (m, 1H), 3.03 (d, *J* = 5.5 Hz, 2H), 1.63−1.56 (m, 1H), 1.33−1.21 (m, 2H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 136.6, 133.5, 128.7, 128.0, 107.6, 59.5, 58.4, 40.9, 40.8, 24.8, 23.4, 22.3; FTIR (neat) 2956, 2923, 2869, 1682, 1565, 1448, 1368, 1330, 1204, 1016, 836, 754, 689 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{16}H_{22}N_3O_5$ 336.1559, found 336.1561; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 254 nm) t_R = 10.3 min (major isomer), 12.5 min (minor isomer).

*(R)-5-Cyclohexyl-3-(3,3-dinitroazetidin-1-yl)-1-phenylpentan-1-one (**3c**).* Yellow oil (77 mg, 99%); $[\alpha]_D^{24}$ −27.6 (*c* 1, $CHCl_3$, 94% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95−7.93 (m, 2H), 7.62−7.59 (m, 1H), 7.50−7.47 (m, 2H), 4.14−4.05 (m, 4H), 3.28−3.23 (m, 1H), 3.08−2.95 (m, 2H), 1.70−1.60 (m, 5H), 1.53−1.46 (m, 1H), 1.43−1.35 (m, 1H), 1.22−1.09 (m, 6H), 0.88−0.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 136.6, 133.5, 128.7, 128.0, 107.5, 60.8, 59.8, 40.3, 37.7, 33.3, 33.1, 32.2, 28.5, 26.5, 26.2, 26.2; FTIR (neat) 2922, 2850, 1683, 1565, 1447, 1370, 1329, 1209, 992, 752, 688 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{20}H_{28}N_3O_5$ 390.2029, found 390.2032; HPLC (Chiralcel OD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 254 nm) t_R = 9.4 min (minor isomer), 11.5 min (major isomer).

*(R)-3-(3,3-Dinitroazetidin-1-yl)-1,5-diphenylpentan-1-one (**3d**).* Yellow oil (60 mg, 78%); $[\alpha]_D^{23}$ −29.7 (*c* 1, $CHCl_3$, 92% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94−7.92 (m, 2H), 7.62−7.59 (m, 1H), 7.50−7.47 (m, 2H), 7.28−7.25 (m, 2H), 7.19−7.16 (m, 1H), 7.14−7.12 (m, 2H), 4.14−4.05 (m, 4H), 3.38−3.33 (m, 1H), 3.16−3.02 (m, 2H), 2.70−2.58 (m, 2H), 1.86−1.79 (m, 1H), 1.77−1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 141.2, 136.5, 133.6, 128.8, 128.5, 128.2, 128.0, 126.1, 107.4, 60.1, 59.6, 40.0, 33.0, 31.0; FTIR (neat) 3027, 2928, 2863, 1682, 1563, 1448, 1371, 1330, 1204, 1001, 837, 752, 689 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{20}H_{22}N_3O_5$ 384.1559, found 384.1556; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) t_R = 14.3 min (major isomer), 16.0 min (minor isomer).

*(R)-3-(3,3-Dinitroazetidin-1-yl)-1-phenyloct-7-en-1-one (**3e**).* Yellow oil (68 mg, 98%); $[\alpha]_D^{23}$ −30.0 (*c* 1, $CHCl_3$, 94% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95−7.93 (m, 2H), 7.62−7.58 (m, 1H), 7.50−7.47 (m, 2H), 5.78−5.70 (m, 1H), 5.02−4.95 (m, 2H), 4.14−4.06 (m, 4H), 3.31−3.26 (m, 1H), 3.09−2.97 (m, 2H), 2.10−1.99 (m, 2H), 1.54−1.48 (m, 1H), 1.47−1.39 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 137.9, 136.6, 133.5, 128.7, 128.0, 115.1, 107.5, 60.4, 59.8, 40.2, 33.5, 30.6, 23.9; FTIR (neat) 2926, 2857, 1683, 1564, 1448, 1370, 1329, 1210, 1001, 912, 754, 689 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{17}H_{22}N_3O_5$ 348.1559, found 348.1561; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) t_R = 8.8 min (major isomer), 11.0 min (minor isomer).

*(R)-7-(tert-Butyldimethylsilyloxy)-3-(3,3-dinitroazetidin-1-yl)-1-phenylheptan-1-one (**3f**).* Yellow oil (77 mg, 83%); $[\alpha]_D^{24}$ −21.0 (*c* 1, $CHCl_3$, 93% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95−7.93 (m, 2H), 7.61−7.58 (m, 1H), 7.50−7.47 (m, 2H), 4.15−4.06 (m, 4H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.30−3.26 (m, 1H), 3.10−2.95 (m, 2H), 1.50−1.46 (m, 3H), 1.44−1.28 (m, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 136.6, 133.5, 128.7, 128.0, 107.5, 62.5, 60.5, 59.8, 40.2, 32.8, 31.1, 25.9, 21.1, 18.2, −5.3; FTIR (neat) 2929, 2857, 1684, 1567, 1448, 1371, 1330, 1254, 1095, 834, 774, 688 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{22}H_{36}N_3O_6Si$ 466.2373, found 466.2374; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 254 nm) t_R = 6.0 min (major isomer), 6.9 min (minor isomer).

*(R)-6-(Benzyloxy)-3-(3,3-dinitroazetidin-1-yl)-1-phenylhexan-1-one (**3g**).* Yellow oil (68 mg, 80%); $[\alpha]_D^{24}$ −21.3 (*c* 1, $CHCl_3$, 93% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94−7.92 (m, 2H), 7.61−7.58 (m, 1H), 7.49−7.46 (m, 2H), 7.35−7.26 (m, 5H), 4.47 (s, 2H), 4.14−4.04 (m, 4H), 3.45 (t, *J* = 6.0 Hz, 2H), 3.33−3.28 (m, 1H), 3.10−2.96 (m, 2H), 1.69−1.54 (m, 3H), 1.53−1.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 138.2, 136.5, 133.5, 128.7, 128.7, 128.3, 128.0, 127.6, 107.4, 72.9, 69.7, 60.2, 59.7, 40.1, 27.9, 24.9; FTIR (neat) 2924, 2854, 1682, 1564, 1448, 1369, 1330, 1209, 1097, 836, 737, 689 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{22}H_{26}N_3O_6$ 428.1822, found 428.1821; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) t_R = 13.3 min (major isomer), 15.8 min (minor isomer).

*(R)-6-(Benzylthio)-3-(3,3-dinitroazetidin-1-yl)-1-phenylhexan-1-one (**3h**).* Yellow oil (80 mg, 90%); $[\alpha]_D^{24}$ −26.0 (*c* 1, $CHCl_3$, 91% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93−7.91 (m, 2H), 7.62−7.59 (m, 1H), 7.50−7.47 (m, 2H), 7.30−7.26 (m, 4H), 7.23−7.20 (m, 1H), 4.11−4.02 (m, 4H), 3.67 (s, 2H), 3.26−3.22 (m, 1H), 3.01−2.93 (m, 2H), 2.41−2.38 (m, 2H), 1.57−1.48 (m, 3H), 1.47−1.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 138.3, 136.5, 133.6, 128.7, 128.7, 128.4, 128.0, 126.9, 107.4, 60.0, 59.7, 39.8, 36.3, 31.2, 30.1, 24.1; FTIR (neat) 3028, 2924, 2855, 1682, 1563, 1448, 1370, 1329, 1200, 1001, 755, 689 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{22}H_{26}N_3O_5S$ 444.1593, found 444.1594; HPLC (Chiralpak AD-H, hexane/IPA = 88/12, 0.9 mL/min, λ = 254 nm) t_R = 16.1 min (major isomer), 22.7 min (minor isomer).

DOI: 10.1021/acs.joc.5b02124
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*(R)-7-(Dibenzylamino)-3-(3,3-dinitroazetidin-1-yl)-1-phenylheptan-1-one (**3i**).* Yellow oil (82 mg, 77%); $[\alpha]_D^{23}$ −19.3 (*c* 1, $CHCl_3$, 91% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.93−7.91 (m, 2H), 7.61−7.58 (m, 1H), 7.49−7.46 (m, 2H), 7.33−7.25 (m, 8H), 7.22−7.19 (m, 2H), 4.05−3.95 (m, 4H), 3.51 (s, 4H), 3.21−3.16 (m, 1H), 3.02−2.90 (m, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 1.49−1.45 (m, 2H), 1.36−1.29 (m, 2H), 1.28−1.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 139.8, 136.6, 133.5, 128.7, 128.7, 128.1, 128.0, 126.7, 107.5, 60.4, 59.7, 58.4, 52.7, 40.3, 31.0, 27.0, 22.3; FTIR (neat) 3027, 2928, 2859, 1683, 1566, 1449, 1369, 1329, 1208, 1027, 745, 697 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{30}H_{35}N_4O_5$ 531.2607, found 531.2610; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) t_R = 10.4 min (major isomer), 18.5 min (minor isomer).

*(R)-3-(3,3-Dinitroazetidin-1-yl)-1-(4-methoxyphenyl)octan-1-one (**3j**).* Yellow oil (70 mg, 92%); $[\alpha]_D^{23}$ −27.1 (*c* 1, $CHCl_3$, 95% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.94−7.92 (m, 2H), 6.97−6.94 (m, 2H), 4.14−4.04 (m, 4H), 3.88 (s, 3H), 3.28−3.23 (m, 1H), 3.02−2.91 (m, 2H), 1.50−1.43 (m, 1H), 1.39−1.33 (m, 1H), 1.32−1.21 (m, 6H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 163.8, 130.3, 129.7, 113.8, 107.6, 60.9, 59.8, 55.5, 39.9, 31.9, 31.4, 24.5, 22.4, 13.9; FTIR (neat) 2930, 2859, 1672, 1599, 1566, 1460, 1370, 1316, 1259, 1168, 1028, 831 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{18}H_{26}N_3O_6$ 380.1822, found 380.1823; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) t_R = 14.6 min (major isomer), 18.6 min (minor isomer).

*(R)-3-(3,3-Dinitroazetidin-1-yl)-1-(4-fluorophenyl)octan-1-one (**3k**).* Yellow oil (60 mg, 82%); $[\alpha]_D^{23}$ −34.0 (*c* 1, $CHCl_3$, 90% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.00−7.96 (m, 2H), 7.18−7.14 (m, 2H), 4.14−4.05 (m, 4H), 3.28−3.24 (m, 1H), 3.06−2.93 (m, 2H), 1.51−1.44 (m, 1H), 1.40−1.33 (m, 1H), 1.33−1.21 (m, 6H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 165.9 (d, $^1J_{C,F}$ = 255.0 Hz), 133.0 (d, $^4J_{C,F}$ = 3.7 Hz), 130.7 (d, $^3J_{C,F}$ = 8.7 Hz), 115.9 (d, $^2J_{C,F}$ = 22.5 Hz), 107.5, 60.6, 59.8, 40.2, 31.9, 31.3, 24.5, 22.4, 13.9; FTIR (neat) 2931, 2861, 1683, 1597, 1566, 1441, 1371, 1330, 1229, 1156, 991, 834 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{17}H_{23}FN_3O_5$ 368.1622, found 368.1624; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 254 nm) t_R = 14.0 min (major isomer), 15.2 min (minor isomer).

*(R)-3-(3,3-Dinitroazetidin-1-yl)-1-(naphthalen-2-yl)octan-1-one (**3l**).* Yellow oil (69 mg, 86%); $[\alpha]_D^{23}$ −16.3 (*c* 1, $CHCl_3$, 92% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.02−7.97 (m, 2H), 7.93−7.88 (m, 2H), 7.64−7.56 (m, 2H), 4.17−4.09 (m, 4H), 3.35−3.31 (m, 1H), 3.22−3.10 (m, 2H), 1.52−1.49 (m, 1H), 1.45−1.38 (m, 1H), 1.37−1.24 (m, 6H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 135.7, 134.0, 132.4, 129.8, 129.5, 128.7, 128.6, 127.7, 126.9, 123.5, 107.5, 60.8, 59.8, 40.3, 31.9, 31.4, 24.6, 22.4, 13.9; FTIR (neat) 2930, 2860, 1677, 1565, 1467, 1371, 1330, 1179, 1124, 822, 749 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{21}H_{26}N_3O_5$ 400.1872, found 400.1874; HPLC (Chiralpak AD-H, hexane/IPA = 92/8, 0.9 mL/min, λ = 254 nm) t_R = 14.5 min (major isomer), 20.4 min (minor isomer).

*(R)-3-(3,3-Dinitroazetidin-1-yl)-1-(furan-2-yl)octan-1-one (**3m**).* Yellow oil (65 mg, 96%); $[\alpha]_D^{23}$ −27.1 (*c* 1, $CHCl_3$, 92% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 1.5, 0.5 Hz, 1H), 7.23 (dd, *J* = 4.0, 0.5 Hz, 1H), 6.57 (dd, *J* = 3.5, 1.5 Hz, 1H), 4.14−4.06 (m, 4H), 3.20−3.16 (m, 1H), 2.95−2.82 (m, 2H), 1.47−1.42 (m, 1H), 1.39−1.33 (m, 1H), 1.32−1.20 (m, 6H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2, 152.5, 146.7, 117.5, 112.5, 107.5, 60.8, 59.7, 40.0, 31.8, 31.1, 24.4, 22.4, 13.9; FTIR (neat) 2929, 2859, 1671, 1565, 1466, 1372, 1225, 1163, 1014, 883, 762 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{15}H_{22}N_3O_6$ 340.1509, found 340.1508; HPLC (Chiralpak AD-H, hexane/IPA = 92/8, 0.9 mL/min, λ = 254 nm) t_R = 11.0 min (major isomer), 13.3 min (minor isomer).

*(R)-3-(3,3-Dinitroazetidin-1-yl)-1-(furan-3-yl)octan-1-one (**3n**).* Yellow oil (51 mg, 75%); $[\alpha]_D^{23}$ −26.2 (*c* 1, $CHCl_3$, 95% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 1.0, 1.0 Hz, 1H), 7.47 (dd, *J* = 1.5, 1.5 Hz, 1H), 6.77 (dd, *J* = 2.0, 1.0 Hz, 1H), 4.13−4.05 (m, 4H), 3.23−3.18 (m, 1H), 2.86−2.72 (m, 2H), 1.48−1.42 (m, 1H), 1.37−1.21 (m, 7H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 147.3, 144.5, 127.8, 108.4, 107.5, 60.6, 59.8, 42.3, 31.8, 31.3, 24.5, 22.4, 13.9; FTIR (neat) 2930, 2860, 1673, 1563, 1461, 1371, 1329, 1155, 1055, 872, 815, 743 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{15}H_{22}N_3O_6$ 340.1509, found 340.1506; HPLC (Chiralpak AD-H, hexane/IPA = 92/8, 0.9 mL/min, λ = 254 nm) t_R = 11.9 min (major isomer), 16.4 min (minor isomer).

*(R)-3-(3,3-Dinitroazetidin-1-yl)-1-(thiophen-2-yl)octan-1-one (**3o**).* Yellow oil (68 mg, 96%); $[\alpha]_D^{24}$ −30.9 (*c* 1, $CHCl_3$, 94% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.69 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.16 (dd, *J* = 5.0, 4.0 Hz, 1H), 4.14−4.06 (m, 4H), 3.25−3.20 (m, 1H), 3.01−2.89 (m, 2H), 1.49−1.44 (m, 1H), 1.40−1.21 (m, 7H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.0, 143.9, 134.4, 132.2, 128.3, 107.5, 61.0, 59.7, 41.1, 31.8, 31.2, 24.4, 22.4, 13.8; FTIR (neat) 2929, 2858, 1656, 1564, 1461, 1414, 1371, 1331, 1235, 1060, 859, 722 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{15}H_{22}N_3O_5S$ 356.1280, found 356.1277; HPLC (Chiralpak AD-H, hexane/IPA = 92/8, 0.9 mL/min, λ = 254 nm) t_R = 10.6 min (major isomer), 13.4 min (minor isomer).

*(R)-3-(3,3-Dinitroazetidin-1-yl)-1-(thiophen-3-yl)octan-1-one (**3p**).* Yellow oil (64 mg, 90%); $[\alpha]_D^{24}$ −23.1 (*c* 1, $CHCl_3$, 91% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 3.0, 1.5 Hz, 1H), 7.54 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.35 (dd, *J* = 5.0, 3.0 Hz, 1H), 4.14−4.05 (m, 4H), 3.25−3.21 (m, 1H), 3.00−2.87 (m, 2H), 1.49−1.43 (m, 1H), 1.39−1.21 (m, 7H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 142.0, 132.3, 126.8, 126.7, 107.5, 60.7, 59.8, 41.7, 31.9, 31.3, 24.5, 22.4, 13.9; FTIR (neat) 2929, 2859, 1671, 1564, 1412, 1371, 1331, 1225, 1171, 1075, 866, 792 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{15}H_{22}N_3O_5S$ 356.1280, found 356.1280; HPLC (Chiralpak AD-H, hexane/IPA = 92/8, 0.9 mL/min, λ = 254 nm) t_R = 11.5 min (major isomer), 14.6 min (minor isomer).

*(R)-1-Cyclopropyl-3-(3,3-dinitroazetidin-1-yl)octan-1-one (**3q**).* Yellow oil (38 mg, 60%); $[\alpha]_D^{24}$ −31.2 (*c* 1, $CHCl_3$, 91% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 4.10−4.04 (m, 4H), 3.07−3.03 (m, 1H), 2.69−2.55 (m, 2H), 1.95−1.91 (m, 1H), 1.42−1.36 (m, 1H), 1.33−1.21 (m, 7H), 1.06−1.04 (m, 2H), 0.95−0.91 (m, 2H), 0.88 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0, 107.5, 60.5, 59.7, 45.1, 31.9, 31.2, 24.5, 22.4, 21.2, 13.9, 11.4, 11.3; FTIR (neat) 2930, 2860, 1696, 1566, 1442, 1386, 1331, 1195, 1075, 1016, 835 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{14}H_{24}N_3O_5$ 314.1716, found 314.1717; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 220 nm) t_R = 8.3 min (major isomer), 9.8 min (minor isomer).

*(R)-1-Cyclohexyl-3-(3,3-dinitroazetidin-1-yl)octan-1-one (**3r**).* Yellow oil (46 mg, 65%); $[\alpha]_D^{23}$ −24.3 (*c* 1, $CHCl_3$, 90% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 4.09−4.01 (m, 4H), 3.08−3.03 (m, 1H), 2.56−2.42 (m, 2H), 2.36−2.30 (m, 1H), 1.83−1.78 (m, 4H), 1.70−1.67 (m, 1H), 1.39−1.16 (m, 13H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 107.5, 59.9, 59.7, 51.3, 42.3, 31.8, 31.1, 28.4, 28.3, 25.6, 25.5, 25.4, 24.4, 22.4, 13.9; FTIR (neat) 2929, 2856, 1705, 1567, 1449, 1373, 1331, 1145, 909, 835, 731 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{17}H_{30}N_3O_5$ 356.2185, found 356.2187; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 220 nm) t_R = 6.8 min (major isomer), 8.5 min (minor isomer).

*(R)-1-(6-Bromonaphthalen-2-yl)-3-(3,3-dinitroazetidin-1-yl)-5-phenylpentan-1-one (**3s**).* Yellow oil (419 mg, 82%); $[\alpha]_D^{24}$ −28.2 (*c* 1, $CHCl_3$, 91% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.04 (d, *J* = 1.5 Hz, 1H), 8.00 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.81 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.64 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.27−7.24 (m, 2H), 7.18−7.16 (m, 1H), 7.14−7.13 (m, 2H), 4.16−4.07 (m, 4H), 3.42−3.38 (m, 1H), 3.25−3.11 (m, 2H), 2.73−2.61 (m, 2H), 1.89−1.82 (m, 1H), 1.80−1.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 141.1, 136.5, 134.1, 131.0, 130.8, 130.5, 129.9, 129.6, 128.5, 128.2, 127.7, 126.1, 124.7, 123.2, 107.4, 60.1, 59.6, 40.0, 32.9, 31.0; FTIR (neat) 3026, 2925, 2855, 1677, 1563, 1458, 1370, 1331, 1204, 1169, 1063, 881, 810, 749 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{24}H_{23}BrN_3O_5$ 512.0821, found 512.0817; HPLC (Chiralpak AD-H, hexane/IPA = 80/20, 0.9 mL/min, λ = 254 nm) t_R = 20.3 min (major isomer), 27.2 min (minor isomer).

*(R,E)-1-(6-Bromonaphthalen-2-yl)-3-(3,3-dinitroazetidin-1-yl)-5-phenylpentan-1-one Oxime (**4**).* Hydroxylamine hydrochloride (21 mg, 0.3 mmol) was added to a solution of **3s** (102 mg, 0.2 mmol) and pyridine (0.025 mL, 8 M) in EtOH (2 mL, 0.1 M) at rt, and then the mixture was allowed to stir at reflux. After 3 h, the mixture was cooled

DOI: 10.1021/acs.joc.5b02124
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to rt. The mixture was quenched by saturated NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with saturated NH_4Cl and brine and then dried over $MgSO_4$. Filtration, concentration, and purification by flash column chromatography (SiO_2, 15% EtOAc in hexanes) provided the oxime **4** in 66% yield (69 mg, 0.132 mmol) as a white solid: mp 118−119 °C; $[\alpha]_D^{23}$ −1.8 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 8.02 (d, *J* = 1.5 Hz, 1H), 7.98 (s, 1H), 7.81−7.76 (m, 2H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.59 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.21−7.13 (m, 3H), 6.97 (dd, *J* = 8.0, 1.5 Hz, 2H), 4.09 (s, 4H), 3.10−3.01 (m, 3H), 2.71−2.58 (m, 2H), 1.70−1.66 (m, 2H); ^{13}C NMR [125 MHz, $CO(CD_3)_2$] δ 155.9, 142.9, 135.3, 135.2, 132.4, 131.1, 130.2, 130.1, 128.9, 128.8, 127.9, 126.5, 126.2, 125.8, 120.7, 109.2, 62.6, 60.1, 33.4, 31.1, 27.2; FTIR (neat) 3144, 3026, 2857, 1557, 1458, 1371, 1330, 1178, 1028, 973, 824, 749, 699 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ $C_{24}H_{24}BrN_4O_5$ 527.0930, found 527.0928.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02124.

Copies of ^1H and ^{13}C NMR spectra of all new compounds, chiral HPLC analysis data of **3a−3s**, and X-ray crystallographic data of **4** (PDF)

X-ray crystallographic data of **4** in CIF format (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support by DAPA/ADD of Korea and the Converged Energy Materials Research Center in Yonsei University.

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DOI: 10.1021/acs.joc.5b02124
J. Org. Chem. 2015, 80, 11435−11440