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Pyrrolidine-thioxotetrahydropyrimidinone as an efficient organocatalyst for the enantioselective Michael addition of cyclic ketones to nitrodienes

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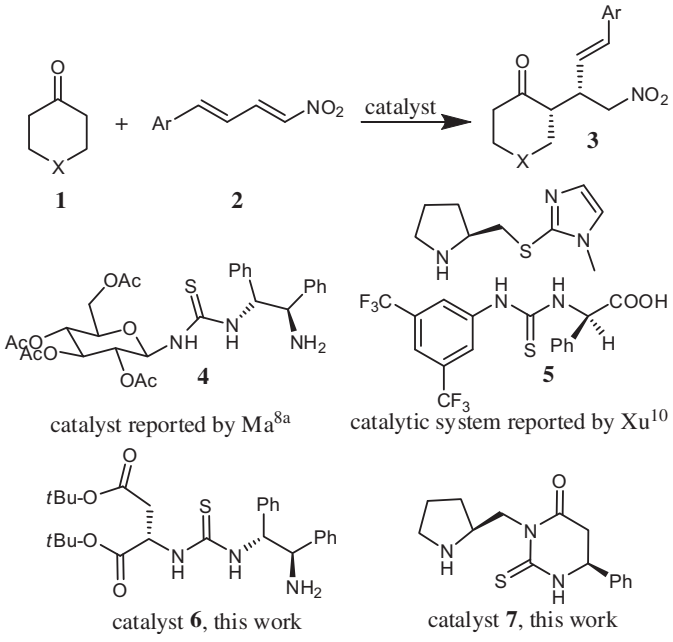
ABSTRACT

Among the various Michael additions, the enantioselective reaction between cyclic ketones and nitrodienes has received little attention in comparison to the corresponding reaction with nitroolefins. A bifunctional organocatalyst consisting of the pyrrolidine moiety and a thioxotetrahydropyrimidinone ring successfully catalyzed this asymmetric transformation. The products of the reaction between various ketones and nitrodienes were obtained in high yields (up to 96%) with excellent diastereo- (up to >98:2 dr) and enantioselectivities (up to 99:1% er).

1. Introduction

Among the various C–C bond-forming reactions in modern asymmetric catalysis, the Michael addition possesses a pivotal role.[1] With the recognition of organocatalysis as the third branch of asymmetric catalysis, alongside transition metal complexes catalysis and biocatalysis,[2,3] a significant increase in the number of studies concerning Michael additions has been realized. Proline and proline derivatives possess a prominent position among the organocatalysts utilized.[4] The five-membered secondary amine of the pyrrolidine ring enables the activation of carbonyl compounds through the formation of enamine intermediates, while incorporation of a chiral template provides extra interactions or a bulky environment leading to enhanced selectivity.

The Michael reaction between carbonyl compounds and nitrostyrenes has been extensively studied.[5] In contrast, the use of nitrodienes as the Michael acceptor remains an unexplored area of research.[6] Alexakis and co-workers succeeded in developing the asymmetric Michael addition of aldehydes to nitrodienes,[7] while more recently, we and others have disclosed the asymmetric reaction between aromatic methyl ketones with nitrodienes.[6e,n,8] Although there are several examples demonstrating the conjugate addition of cyclohexanone to phenyl nitrodiene **2a**,[9] to the best of our knowledge, only two reports study further the reaction between cyclic ketones and nitrodienes, with limited examples regarding the substrate scope (Scheme 1).[8a,10]



Scheme 1. Organocatalysts for the addition of cyclic ketones to nitrodienes.

Catalysts usually performing well in the reaction between methyl ketones and nitrodienes suffer from poor catalytic activity when cyclic

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ketones replace methyl ketones.[8a] Thus, Ma and co-workers had to alter the structural characteristics of their catalyst in order to find catalyst **4** to perform well in the above mentioned reaction (Scheme 1).[8a] On the other hand, Xu and co-workers used a pyrrolidine-derived catalyst in combination with a chiral thiourea additive as a highly efficient catalytic system for the same transformation (catalytic system **5**, Scheme 1).[10] The thiourea additive had a great impact in both yield and selectivity of the reaction. During the preparation of this manuscript, Wu and He presented a slight modification of Ma's catalyst as an efficient catalyst for this reaction.[11]

On the basis of our own experience on organocatalytic Michael additions[5f,j,6n,12a,b] and organocatalysis in general,[12c–e] we initiated our studies for the reaction between cyclohexanone (**1a**) and phenyl nitrodiene (**2a**) utilizing catalyst **6**, which was the catalyst of choice for the Michael addition of methyl ketones to nitroolefins.[6n] However, it became immediately obvious that the reaction suffered from low yield and diastereoselectivity (13% yield, 70:30 dr, −99:1% er). Therefore, taking into account the excellent catalytic activity of the pyrrolidine-thioxotetrahydropyrimidinone **7** for the addition of cyclic ketones to nitroalkenes,[12b] and for other difficult organocatalytic transformations,[12d] we hypothesized that this bifunctional catalyst could activate cyclic ketones via enamine formation with its secondary amine, and simultaneously nitrodienes via hydrogen bonding. Moreover, one of our objectives was to extend the substrate scope of this elegant protocol. The results of our study are discussed in the present work.

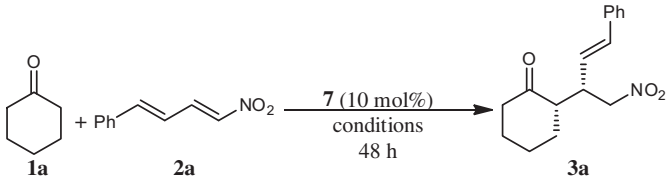
2. Results and discussion

We initiated our studies using as a model reaction the addition of cyclohexanone (**1a**) to phenyl nitrodiene (**2a**), in the presence of catalyst **7** (10 mol %), 4-nitrobenzoic acid (10 mol %), and H_2O (2 equiv) as additives. Although nitrodiene **2a** can be theoretically attacked in either the β- or δ-position, only the 1,4-addition product **3a** was obtained showcasing the regioselectivity of this reaction, which is in accordance with literature.[8,10] A screening of various solvents revealed that both polar and non-polar solvents led generally to high yields and excellent diastereoselectivities and enantioselectivities (entries 1–12, Table 1). Toluene was found to be the best solvent in terms of yield and selectivity (entry 1, Table 1). In the absence of water as additive, the reaction yield was maintained high but the selectivity was very slightly decreased (entry 13, Table 1), while in the absence of both water and the acidic co-catalyst, only traces of the product were obtained (entry 14, Table 1).

To further demonstrate the importance of the acidic counterpart in the catalytic cycle, several Bronsted acids were tested in place of 4-nitrobenzoic acid (Table 2). 4-Cyanobenzoic acid, with a similar pK_a [pK_a values in H_2O of 4-nitrobenzoic acid (3.44), 4-cyanobenzoic acid (3.55)], provided high selectivity but lower yield (entry 1, Table 2), while weaker acids like benzoic and acetic acid had a negative impact on both reactivity and enantioselectivity (entries 2 and 3, Table 2). In the presence of a strong acid like TFA, only traces of the product were obtained, probably due to salt formation with the amine functionality of the catalyst (entry 4, Table 2). Moreover, when the catalyst loading was decreased from 10 to 5 mol %, or the ratio of ketone to nitrodiene to 5:1, the reaction turned sluggish (entries 5 and 6, Table 2).

With optimal conditions in hand, we set out to test the scope and limitations of our catalyst. A variety of substituted aromatic nitrodienes (**2b**–**d**) were utilized (entries 2–4, Table 3). All reactions with cyclohexanone provided the product almost as a single diastereoisomer (dr >95:5). Electron-donating and electron-withdrawing groups are well tolerated, affording the desired products **3b**–**d** in high yields and excellent selectivities. When nitrodiene **2e** was used, the yield and the selectivity dropped slightly (entry 5, Table 3). A variety of six-membered cyclic ketones were studied (entries 6–10, Table 3). 4-Methyl cyclohexanone provided the product in high yield and enantioselectivity, but in poor diastereoselectivity (entry 6, Table 3). This reaction generates three stereogenic centers deriving from the desymmetrization of the 4-substituted ketone. Although the two stereogenic centers deriving from the conjugate addition seem to be excellently controlled by the catalyst providing the product in an excellent *syn* configuration, the third stereocenter at the 4-position of the six-membered ring was not controlled since it seems to be too far away from the catalytic center. Thus, only two diastereomers are

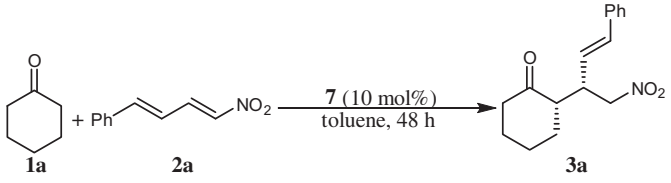
Table 1
Enantioselective Michael addition of cyclohexanone to phenyl nitrodiene using catalyst **7**



Entry	Solvent	Additives	Yield[a] (%)	er[b] (%)	dr[c]
1	Toluene	4-NBA, H_2O	93	98.5:1.5	98:2
2	Benzene	4-NBA, H_2O	84	97.5:2.5	97:3
3	Xylene	4-NBA, H_2O	79	97:3	82:18
4	Et_2O	4-NBA, H_2O	92	97:3	96:4
5	CH_3CN	4-NBA, H_2O	91	98:2	96:4
6	MeOH	4-NBA, H_2O	94	96:4	95:5
7	DMSO	4-NBA, H_2O	85	92:8	93:7
8	EtOAc	4-NBA, H_2O	90	97:3	97:3
9	DCE	4-NBA, H_2O	91	98:2	95:5
10	$CHCl_3$	4-NBA, H_2O	95	98:2	97:3
11	CH_2Cl_2	4-NBA, H_2O	92	98:2	96:4
12[d]	THF	4-NBA, H_2O	94	96:4	96:4
13	Toluene	4-NBA	96	97:3	95:5
14[e]	Toluene	—	Traces	—	—

4-NBA: 4-nitrobenzoic acid, DCE: 1,2-dichloroethane.
[a] Isolated yield.
[b] The enantiomeric ratio (er) was determined by chiral HPLC.
[c] The diastereomeric ratio (dr) was determined by ^{1}H NMR of the crude reaction mixture.
[d] Reaction time 72 h.
[e] Reaction time 6 days.

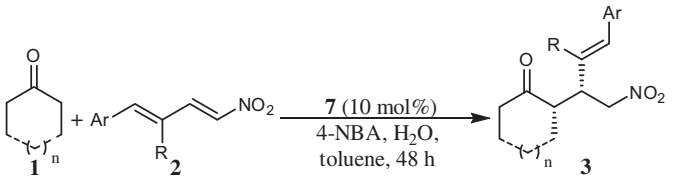
Table 2
Effect of the acid additive on the Michael addition of cyclohexanone to phenyl nitrodiene

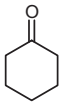
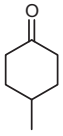
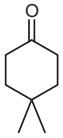
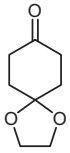
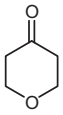
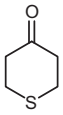
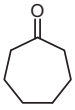


Entry	Additives	Yield[a] (%)	er[b] (%)	dr[c]
1	4-CBA, H_2O	79	97.5:2.5	97:3
2	PhCOOH, H_2O	32	92:8	96:4
3	AcOH, H_2O	86	96.5:3.5	90:10
4	TFA, H_2O	Traces	—	—
5[d]	4-NBA, H_2O	43	97:3	97:3
6[e]	4-NBA, H_2O	54	98:2	97:3

4-NBA: 4-nitrobenzoic acid, 4-CBA: 4-cyanobenzoic acid, AcOH: acetic acid, TFA: trifluoroacetic acid.
[a] Isolated yield.
[b] The enantiomeric ratio (er) was determined by chiral HPLC.
[c] The diastereomeric ratio (dr) was determined by ^{1}H NMR of the crude reaction mixture.
[d] Catalyst (5 mol %) was used.
[e] Ratio of ketone to nitrodiene 5:1.

Table 3
Enantioselective Michael reaction between cyclic ketones and nitrodienes using catalyst **7**[a]



Entry	Ketone	Ar, R	Yield[b] (%)	er[c] (%)	dr[d]
1		Ph, H (**2a**)	93 (**3a**)	98.5:1.5	98:2
2		*o*-NO_2Ph, H (**2b**)	91 (**3b**)	99:1	>98:2
3		*p*-ClPh, H (**2c**)	92 (**3c**)	98:2	96:4
4[e]		*p*-MeOPh, H (**2d**)	73 (**3d**)	97.5:2.5	>98:2
5[e]		Ph, Me (**2e**)	80 (**3e**)	98:2	95:5
6		Ph, H (**2a**)	82 (**3f**)	98:2	58:42
7[e,f]		Ph, H (**2a**)	57 (**3g**)	90:10	90:10
8		Ph, H (**2a**)	73 (**3h**)	98:2	70:30
9[e,f]		Ph, H (**2a**)	74 (**3i**)	96.5:3.5	73:27
10[e,f]		Ph, H (**2a**)	83 (**3j**)	94:6	97:3
11		Ph, H (**2a**)	80 (**3k**)	86.5:13.5	90:10
12		Ph, H (**2a**)	90 (**3l**)	93:7	56:44
13		*o*-NO_2Ph, H (**2b**)	76 (**3m**)	96:4	85:15
14		*p*-ClPh, H (**2c**)	90 (**3n**)	95:5	70:30
15[e]		*p*-MeOPh, H (**2d**)	83 (**3o**)	94:6	70:30
16		Ph, Me (**2e**)	93 (**3p**)	96.5:3.5	80:20

[a] Reactions were performed using catalyst **7** (10 mol %), nitrodiene (0.1 mmol), ketone (1 mmol), 4-nitrobenzoic acid (10 mol %), and H_2O (2 equiv) in toluene (0.25 mL) for 48 h at room temperature.
[b] Isolated yield.
[c] The enantiomeric ratio (er) was determined by chiral HPLC.
[d] The diastereomeric ratio (dr) was determined by ^1H NMR of the crude reaction mixture.
[e] Reaction time 72 h.
[f] 20% catalyst loading was used.

obtained and their ratio reflects the diastereoselectivity at the 4-position of the six-membered ring. When 4,4-disubstituted cyclohexanones were employed, the product was obtained in lower yields and varying selectivities (entries 7 and 8, Table 3). These results highlight the fact that by adding substituents in the 4-position of the six-membered ring, you are bound to have undesired steric repulsions that lead to lower yields and selectivities. Tetrahydropyran-4-one and tetrahydrothiopyran-4-one proved to be difficult substrates in the Michael reaction with phenyl nitrodiene **2a** and required higher catalyst loading in order to deliver the products in good yields (entries 9 and 10, Table 3). Cycloheptanone and cyclopentanone, which are known to be 'difficult' substrates in enamine activation reactions and usually suffer from low yields and selectivities, were also utilized with some success (entries 11 and 12, Table 3). Moreover, in order to broaden the scope of this methodology, we investigated the reaction of cyclopentanone with a variety of substituted nitrodienes (**2a**–**e**, entries 12–16, Table 3). In all cases, high to excellent yields, medium to high diastereoselectivities, and high enantioselectivities were observed.

A plausible transition-state model is proposed in Fig. 1. The secondary amine of the pyrrolidine ring activates the ketone through the formation of an enamine intermediate. The *s*-trans conformation is preferred to the *s*-cis, since it lacks the undesired steric repulsions the latter suffers from. Simultaneously, the thioxotetrahydropyrimidinone ring of the catalyst provides steric shielding as well as hydrogen bond interactions with the nitro group of the nitrodiene, thus guiding the attack just from the one face leading to high enantiocontrol. When R=H, the product is provided in high diastereo- and enantioselectivity. However, when steric bulkiness is added by placing one or two substituents at the 4-position of the six-membered ring (R≠H), then additional repulsions are created with the backbone of the nitrodiene. When cyclic ketones of other size are utilized, the conformation of the enamine is slightly modified leading to lower levels of selectivity. Thus, we may predict that six-member ring ketones bearing substituents at the 4-position, as well as five- or seven-member ring ketones will not perform well in this transformation leading to lower selectivities. On the other hand, six-member ketones will provide the product in excellent yields and selectivities.

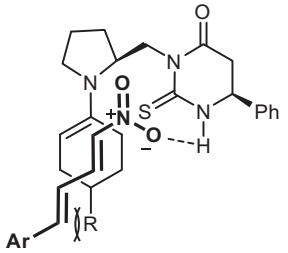


Fig. 1. Proposed transition-state of the model reaction.

3. Conclusions

In conclusion, pyrrolidine-thioxotetrahydropyrimidinone **7** was found to be an excellent catalyst for the less-studied reaction between cyclic ketones and substituted nitrodienes. When cyclohexanone was employed, excellent yields and selectivities were obtained, while other cyclic ketones can be successfully utilized. Efforts to further expand the utility of catalyst **7** are under way.

4. Experimental section

4.1. General information

Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of

products was accomplished using forced-flow chromatography on Merck Kieselgel 60 F_{254} 230–400 mesh. Thin-layer chromatography (TLC) was performed on aluminum-backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid. Melting points were determined on a Büchi 530 hot stage apparatus and are uncorrected. IR spectra were recorded on a Nicolet IR200 FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on Varian Mercury (200 or 50 MHz) as noted, and are internally referenced to residual solvent signals ($CDCl_3$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, br s=broad signal, br s m=broad signal multiplet), coupling constant, integration, and assignment. Diastereomeric ratios were determined by ^1H NMR spectra (200 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm). Mass spectra were recorded on a Finnigan Surveyor MSQ Plus, with only molecular ions and major peaks being reported with intensities quoted as percentages of the base peak. High Performance Liquid Chromatography (HPLC) was used to determine enantiomeric excesses and was performed on an Agilent 1100 Series apparatus using Chiralpak® AD-H, OD-H, and AS-H columns. Optical rotations were measured on a Perkin–Elmer 343 polarimeter. The configuration of the products has been assigned either by comparison to literature data or by analogy.

4.2. General procedure for the synthesis of nitrodienes

The nitrodienes used in this study were known compounds, except nitrodiene **2e**, which was prepared according to literature.[6n]

*4.2.1. (2-Methyl-4-nitrobuta-1,3-dienyl)benzene (**2e**).* Orange solid (22% for two steps, *E*/*Z* mixture: 5:1); mp 85–86 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 7.81 (d, *J*=13.3 Hz, 1H, =CH), 7.46–7.33 (m, 5H, ArH), 7.19 (d, *J*=13.3 Hz, 1H, =CH), 7.05 (s, 1H, =CH), 2.08 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.4, 144.0, 137.2, 136.6, 135.7, 129.7, 128.8, 128.5, 14.1; MS (ESI) *m*/*z* (%): 190 $[M+H, (20)]^+$.

4.3. General procedure for the Michael reaction between ketones and nitrodienes

To a stirring solution of catalyst **7** (0.01 mmol) in dry toluene (0.25 mL), 4-nitrobenzoic acid (2 mg, 0.01 mmol) and H_2O (4 μL, 0.20 mmol) were added. Nitrodiene (0.10 mmol) was added followed by ketone (1.00 mmol). The reaction mixture was left stirring for the stated time. The solvent was evaporated and the crude product was purified using flash column chromatography eluting with various mixtures of petroleum ether (40–60 °C)/EtOAc to afford the desired product.

4.4. Characterization of the products

*4.4.1. (S)-2-[(S,E)-1-Nitro-4-phenylbut-3-en-2-yl]cyclohexanone (**3a**).*[8a] White solid (93%); mp 120–122 °C [lit.: mp 111–112 °C];[8a] $[\alpha]_D^{20}$ −63.2 (*c* 0.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.18 (m, 5H, ArH), 6.49 (d, *J*=15.8 Hz, 1H, =CH), 6.01 (dd, *J*=15.8, 9.5 Hz, 1H, =CH), 4.67 (dd, *J*=11.9, 5.0 Hz, 1H, C*H*HNO_2), 4.56 (dd, *J*=11.9, 8.2 Hz, 1H, C*H*HNO_2), 3.42–3.27 (m, 1H, CH), 2.60–2.30 (m, 3H, COCH and COCHH), 2.21–2.03 (m, 2H, 2× C*H*H), 1.96–1.82 (m, 1H, C*H*H), 1.73–1.54 (m, 3H, 3× C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.2, 136.2, 134.4, 128.5, 127.9, 126.4, 125.6, 78.0, 51.6, 42.6, 41.9, 32.6, 28.1, 25.0; MS (ESI) *m*/*z* (%): 274 $[M+H, (100)]^+$; HPLC analysis: 98.5:1.5 er, 98:2 dr; Diacel Chiralpak® AS-H column, hexane/2-propanol: 85:15, flow rate 0.8 mL/min, t_R=12.59 min (minor) and 19.70 min (major).

*4.4.2. (S)-2-[(S,E)-1-Nitro-4-(2-nitrophenyl)but-3-en-2-yl]cyclohexanone (**3b**).*[8a] Yellow oil (91%); $[\alpha]_D^{20}$ −41.3 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.96 (d, *J*=7.8 Hz, 1H, ArH), 7.61–7.36 (m, 3H, ArH), 6.96 (d, *J*=15.7 Hz, 1H, =CH), 6.01 (dd, *J*=15.7, 9.4 Hz, 1H, =CH), 4.76–4.79 (m, 2H, $CHHNO_2$), 3.49–3.31 (m, 1H, CH), 2.66–2.54 (m, 1H, COCH), 2.49–2.32 (m, 2H, COCHH), 2.28–2.04 (m, 2H, 2× C*H*H), 1.98–1.89 (m, 1H, C*H*H), 1.80–1.47 (m, 3H, 3× C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.2, 147.3, 133.4, 132.5, 131.2, 130.2, 129.3, 128.5, 124.5, 77.6, 51.5, 42.6, 41.9, 32.6, 28.1, 25.1; MS (ESI) *m*/*z* (%): 319 $[M+H, (20)]^+$; HPLC analysis: 99:1 er, >98:2 dr; Diacel Chiralpak® OD-H column, hexane/2-propanol: 95:5, flow rate 0.8 mL/min, t_R=34.56 min (minor) and 36.46 min (major).

*4.4.3. (S)-2-[(S,E)-4-(4-Chlorophenyl)-1-nitrobut-3-en-2-yl]cyclohexanone (**3c**).*[10] White solid (92%); mp 118–119 °C [lit.: mp 125–126 °C];[10] $[\alpha]_D^{20}$ −47.4 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.26–7.24 (m, 4H, ArH), 6.44 (d, *J*=15.8 Hz, 1H, =CH), 5.99 (dd, *J*=15.8, 9.5 Hz, 1H, =CH), 4.67 (dd, *J*=11.9, 4.9 Hz, 1H, C*H*HNO_2), 4.55 (dd, *J*=11.9, 8.4 Hz, 1H, C*H*HNO_2), 3.41–3.25 (m, 1H, CH), 2.60–2.33 (m, 3H, COCH and COCHH), 2.20–2.04 (m, 2H, 2× C*H*H), 1.94–1.86 (m, 1H, C*H*H), 1.75–1.58 (m, 2H, 2× C*H*H), 1.53–1.39 (m, 1H, C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.2, 134.6, 133.5, 133.1, 128.7, 127.6, 126.3, 77.9, 51.5, 42.6, 41.9, 32.6, 28.0, 25.0; MS (ESI) *m*/*z* (%): 330 $[M+Na, (100)]^+$, 308 $[M+H, (35)]^+$; HPLC analysis: 98:2 er, 96:4 dr; Diacel Chiralpak® AD-H column, hexane/2-propanol: 95:5, flow rate 0.8 mL/min, t_R=30.07 min (minor) and 33.81 min (major).

*4.4.4. (S)-2-[(S,E)-4-(4-Methoxyphenyl)-1-nitrobut-3-en-2-yl]cyclohexanone (**3d**).*[10] Yellow solid (73%); mp 136–137 °C [lit.: mp 144–145 °C];[10] $[\alpha]_D^{20}$ −61.8 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.26 (d, *J*=8.8 Hz, 2H, ArH), 6.82 (d, *J*=8.8 Hz, 2H, ArH), 6.40 (d, *J*=15.8 Hz, 1H, =CH), 5.83 (dd, *J*=15.8, 9.6 Hz, 1H, =CH), 4.64 (dd, *J*=11.8, 4.9 Hz, 1H, C*H*HNO_2), 4.52 (dd, *J*=11.8, 8.3 Hz, 1H, C*H*HNO_2), 3.77 (s, 3H, OCH_3), 3.37–3.21 (m, 1H, CH), 2.57–2.29 (m, 3H, COCH and COCHH), 2.22–2.00 (m, 2H, 2× C*H*H), 1.93–1.79 (m, 1H, C*H*H), 1.73–1.55 (m, 3H, 3× C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.5, 159.3, 133.8, 128.9, 127.6, 123.2, 113.9, 78.2, 55.3, 51.6, 42.6, 42.0, 32.6, 28.1, 25.0; MS (ESI) *m*/*z* (%): 326 $[M+Na, (100)]^+$, 304 $[M+H, (60)]^+$; HPLC analysis: 97.5:2.5 er, >98:2 dr; Diacel Chiralpak® AD-H column, hexane/2-propanol: 95:5, flow rate 0.8 mL/min, t_R=41.35 min (minor) and 46.42 min (major).

*4.4.5. (S)-2-[(R,E)-3-Methyl-1-nitro-4-phenylbut-3-en-2-yl]cyclohexanone (**3e**).* Colorless oil (80%); $[\alpha]_D^{20}$ −40.6 (*c* 1.0, $CHCl_3$); IR (film) 2942, 2861, 1707, 1550, 1446, 1381, 1129, 745, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.10 (m, 5H, ArH), 6.39 (s, 1H, =CH), 4.82 (dd, *J*=11.2, 4.2 Hz, 1H, C*H*HNO_2), 4.42 (t, *J*=11.2 Hz, 1H, C*H*HNO_2), 3.34 (td, *J*=11.2, 4.2 Hz, 1H, CH), 2.54–2.32 (m, 3H, COCH and COCHH), 2.14–1.99 (m, 2H, 2× C*H*H), 1.91–1.61 (m, 6H, 3× C*H*H and CH_3), 1.56–1.41 (m, 1H, C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.0, 136.8, 132.6, 131.4, 128.9, 128.1, 126.7, 76.9, 49.8, 48.0, 42.7, 33.0, 28.5, 24.9, 13.8; MS (ESI) *m*/*z* (%): 288 $[M+H, (100)]^+$; HRMS exact mass calculated for $[M+H]^+$ ($C_{17}H_{22}NO_3$) requires *m*/*z* 288.1594, found *m*/*z* 288.1586; HPLC analysis: 98:2 er, 95:5 dr; Diacel Chiralpak® AD-H column, hexane/2-propanol: 98:2, flow rate 0.8 mL/min, t_R=30.46 min (minor) and 35.32 min (major).

*4.4.6. (2S)-4-Methyl-2-[(S,E)-1-nitro-4-phenylbut-3-en-2-yl]cyclohexanone (**3f**).* Yellow oil (82%); $[\alpha]_D^{20}$ −37.4 (*c* 1.0, $CHCl_3$); IR (film) 2924, 1708, 1550, 1448, 1380, 1131, 971, 747, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.33–7.25 (m, 5H, ArH), 6.56–6.43 (m, 1H, =CH), 6.27 (dd, *J*=15.9, 9.1 Hz, 0.42H, =CH), 5.92 (dd, *J*=15.8, 9.5 Hz,

0.58H, =CH), 4.71–4.62 (m, 1H, C*H*HNO$_2$), 4.54–4.40 (m, 1H, C*H*HNO$_2$), 3.46–3.27 (m, 0.58H, CH), 3.23–3.08 (m, 0.42H, CH), 2.72–2.34 (m, 3H, COCH and COCHH), 2.16–1.86 (m, 2H, 2× C*H*H), 1.84–1.61 (m, 2H, 2× C*H*H), 1.44–1.18 (m, 1H, CH), 1.09 (d, *J*=6.8 Hz, 1.8H, CH$_3$), 0.99 (d, *J*=6.1 Hz, 1.2H, CH$_3$); ^{13}C NMR (50 MHz, CDCl$_3$): δ 212.3, 210.9, 136.0, 134.9, 134.8, 128.6, 128.5, 128.0, 126.5, 125.3, 124.9, 78.2, 78.0, 50.7, 48.5, 43.9, 42.3, 41.8, 39.8, 38.4, 37.6, 35.1, 33.8, 32.0, 26.5, 21.2, 19.3; MS (ESI) *m*/*z* (%): 288 [M+H, (100)]$^+$; HRMS exact mass calculated for [M+H]$^+$ (C$_{17}$H$_{22}$NO$_3$) requires *m*/*z* 288.1594, found *m*/*z* 288.1587; HPLC analysis: 98:2 er, 58:42 dr; Diacel Chiralpak® AS-H column, hexane/2-propanol: 95:5, flow rate 0.5 mL/min, t_R=25.49 min (minor) and 29.62 min (major).

*4.4.7. (S)-4,4-Dimethyl-2-[(S,E)-1-nitro-4-phenylbut-3-en-2-yl]cyclohexanone (**3g**).* Yellow oil (57%); $[\alpha]_D^{20}$ −22.5 (*c* 1.0, CHCl$_3$); IR (film) 2956, 2925, 2856, 1708, 1551, 1448, 1379, 970, 749, 694 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.40–7.20 (m, 5H, ArH), 6.46 (d, *J*=15.8 Hz, 1H, =CH), 6.25 (dd, *J*=15.9, 9.1 Hz, 0.10H, =CH), 5.99 (dd, *J*=15.8, 9.5 Hz, 0.90H, =CH), 4.68 (dd, *J*=11.8, 5.2 Hz, 1H, C*H*HNO$_2$), 4.56 (dd, *J*=11.8, 8.1 Hz, 1H, C*H*HNO$_2$), 3.38–3.23 (m, 0.90H, CH), 3.16–3.02 (m, 0.10H, CH), 2.74–2.59 (m, 1H, COCH), 2.56–2.40 (m, 1H, COC*H*H), 2.33–2.22 (m, 1H, COC*H*H), 1.84–1.53 (m, 4H, 4× C*H*H), 1.19 (s, 3H, CH$_3$), 0.99 (s, 3H, CH$_3$); ^{13}C NMR (50 MHz, CDCl$_3$): δ 211.8, 136.2, 135.0, 134.3, 128.6, 127.9, 126.5, 125.6, 78.0, 47.1, 44.8, 41.7, 40.1, 38.9, 31.3, 31.0, 24.4; MS (ESI) *m*/*z* (%): 302 [M+H, (100)]$^+$; HRMS exact mass calculated for [M+H]$^+$ (C$_{18}$H$_{24}$NO$_3$) requires *m*/*z* 302.1751, found *m*/*z* 302.1744; HPLC analysis: 90:10 er, 90:10 dr; Diacel Chiralpak® AD-H column, hexane/2-propanol: 99:1, flow rate 0.4 mL/min, t_R=58.05 min (major) and 66.82 min (minor).

*4.4.8. (S)-7-[(S,E)-1-Nitro-4-phenylbut-3-en-2-yl]-1,4-dioxaspiro[4.5]decan-8-one (**3h**).* Yellow oil (73%); $[\alpha]_D^{20}$ −12.7 (*c* 1.0, CHCl$_3$); IR (film) 2961, 2360, 2340, 1714, 1551, 1436, 1379, 1130, 1042, 973, 695 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.41–7.07 (m, 5H, ArH), 6.53–6.42 (m, 1H, =CH), 6.23 (dd, *J*=15.9, 9.2 Hz, 0.32H, =CH), 5.97 (dd, *J*=15.8, 9.5 Hz, 0.68H, =CH), 4.83–4.43 (m, 2H, CHHNO$_2$), 4.10–3.85 (m, 4H, 4× OC*H*H), 3.52–3.28 (m, 0.68H, CH), 3.18–3.05 (m, 0.32H, CH), 2.98–2.83 (m, 1H, COCH), 2.76–2.60 (m, 1H, COC*H*H), 2.54–2.35 (m, 2H, COC*H*H and C*H*H), 2.19–1.79 (m, 3H, 3× C*H*H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 209.7, 209.5, 136.1, 135.4, 134.8, 128.5, 128.0, 126.5, 124.9, 124.1, 107.2, 107.0, 78.1, 77.9, 64.9, 64.7, 64.6, 47.8, 47.3, 43.8, 41.3, 39.0, 38.6, 38.5, 38.2, 34.7, 33.8; MS (ESI) *m*/*z* (%): 332 [M+H, (100)]$^+$; HRMS exact mass calculated for [M+H]$^+$ (C$_{18}$H$_{22}$NO$_5$) requires *m*/*z* 332.1492, found *m*/*z* 332.1483; HPLC analysis: 98:2 er, 70:30 dr; Diacel Chiralpak® AD-H column, hexane/2-propanol: 95:5, flow rate 0.7 mL/min, t_R=46.57 min (minor) and 48.98 min (major).

*4.4.9. (R)-2-[(S,E)-1-Nitro-4-phenylbut-3-en-2-yl]-tetrahydropyrane-4-one (**3i**).*[10] White solid (74%); mp 124–125 °C [lit.: mp 125–126 °C];[8a] $[\alpha]_D^{20}$ −40.4 (*c* 1.0, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.33–7.25 (m, 5H, ArH), 6.57–6.43 (m, 1H, =CH), 6.21 (dd, *J*=15.8, 9.4 Hz, 0.30H, =CH), 5.93 (dd, *J*=15.8, 9.7 Hz, 0.70H, =CH), 4.78–4.61 (m, 1.30H, C*H*HNO$_2$), 4.52 (dd, *J*=12.1, 8.7 Hz, 0.70H, C*H*HNO$_2$), 4.23–4.10 (m, 2H, 2× OC*H*H), 3.83–3.33 (m, 3H, 2× OC*H*H and CH), 2.88–2.34 (m, 3H, COCH and COCHH); ^{13}C NMR (50 MHz, CDCl$_3$): δ 212.6, 137.1, 136.0, 135.2, 129.4, 128.7, 127.7, 126.5, 78.8, 52.5, 43.7, 33.6, 28.8, 25.5; MS (ESI) *m*/*z* (%): 298 [M+Na, (100)]$^+$, 276 [M+H, (15)]$^+$; HPLC analysis: 96.5:3.5 er, 73:27 dr; Diacel Chiralpak® AD-H column, hexane/2-propanol: 90:10, flow rate 1.0 mL/min, t_R=26.75 min (minor) and 36.61 min (major).

*4.4.10. (S)-3-[(S,E)-1-Nitro-4-phenylbut-3-en-2-yl]-tetrahydrothiopyran-4-one (**3j**).*[10] White solid (83%); mp 115–116 °C [lit.: mp 116–118 °C];[8a] $[\alpha]_D^{20}$ −82.8 (*c* 1.0, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.40–7.19 (m, 5H, ArH), 6.54 (d, *J*=15.8 Hz, 1H, =CH), 5.93 (dd, *J*=15.8, 9.7 Hz, 1H, =CH), 4.69–4.43 (m, 2H, CHHNO$_2$), 3.58–3.42 (m, 1H, CH), 3.06–2.65 (m, 7H, COCH, COCHH and 4× SC*H*H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 211.1, 136.5, 136.1, 129.6, 129.2, 127.8, 125.5, 78.1, 54.9, 45.8, 42.7, 35.9, 31.8; MS (ESI) *m*/*z* (%): 314 [M+Na, (50)]$^+$, 292 [M+H, (40)]$^+$; HPLC analysis: 94:6 er, 97:3 dr; Diacel Chiralpak® AD-H column, hexane/2-propanol: 90:10, flow rate 1.0 mL/min, t_R=23.26 min (minor) and 32.37 min (major).

*4.4.11. (S)-2-[(S,E)-1-Nitro-4-phenylbut-3-en-2-yl]cycloheptanone (**3k**).* Yellow oil (80%); $[\alpha]_D^{20}$ −47.8 (*c* 1.0, CHCl$_3$); IR (film) 2922, 2856, 2358, 1697, 1549, 1448, 1378, 970, 748, 693 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.45–7.20 (m, 5H, ArH), 6.50 (d, *J*=15.8 Hz, 1H, =CH), 6.13 (dd, *J*=15.8, 9.5 Hz, 0.10H, =CH), 5.98 (dd, *J*=15.8, 8.9 Hz, 0.90H, =CH), 4.72–4.45 (m, 2H, CHHNO$_2$), 3.33–3.18 (m, 1H, CH), 2.79–2.70 (m, 1H, COCH), 2.61–2.39 (m, 2H, COCHH), 2.03–1.81 (m, 4H, 4× C*H*H), 1.62–1.13 (m, 4H, 4× C*H*H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 214.4, 136.1, 134.8, 128.6, 128.0, 126.4, 125.5, 78.0, 52.7, 43.8, 43.7, 29.7, 28.9, 28.7, 23.7; MS (ESI) *m*/*z* (%): 288 [M+H, (100)]$^+$; HRMS exact mass calculated for [M+H]$^+$ (C$_{17}$H$_{22}$NO$_3$) requires *m*/*z* 288.1594, found *m*/*z* 288.1589; HPLC analysis: 86.5:13.5 er, 90:10 dr; Diacel Chiralpak® AD-H column, hexane/2-propanol: 98:2, flow rate 0.5 mL/min, t_R=46.79 min (minor) and 54.49 min (major).

*4.4.12. (S)-2-[(S,E)-1-Nitro-4-phenylbut-3-en-2-yl]cyclopentanone (**3l**).*[10] White solid (90%); mp 125–126 °C [lit.: mp 122–123 °C];[8a] $[\alpha]_D^{20}$ −80.2 (*c* 1.0, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.39–7.16 (m, 5H, ArH), 6.57–6.44 (m, 1H, =CH), 5.93 (dd, *J*=15.8, 9.3 Hz, 1H, =CH), 4.98–4.67 (m, 1.44H, C*H*HNO$_2$), 4.54 (dd, *J*=12.1, 9.0 Hz, 0.56H, C*H*HNO$_2$), 3.46–3.24 (m, 1H, CH), 2.42–1.96 (m, 5H, 5× C*H*H), 1.89–1.67 (m, 2H, 2× C*H*H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 218.2, 136.0, 135.7, 134.6, 128.6, 128.1, 128.0, 126.5, 126.4, 124.4, 123.7, 77.9, 77.7, 50.1, 49.7, 42.7, 41.9, 39.2, 38.5, 27.4, 26.9, 20.8, 20.5; MS (ESI) *m*/*z* (%): 260 [M+H, (35)]$^+$; HPLC analysis: 93:7 er, 56:44 dr; Diacel Chiralpak® AD-H column, hexane/2-propanol: 93:7, flow rate 1.0 mL/min, t_R=16.47 min (minor) and 20.57 min (major).

*4.4.13. (S)-2-[(S,E)-1-Nitro-4-(2-nitrophenyl)but-3-en-2-yl]cyclopentanone (**3m**).* Yellow oil (76%); $[\alpha]_D^{20}$ −51.8 (*c* 1.0, CHCl$_3$); IR (film) 2964, 2917, 2879, 1731, 1554, 1521, 1379, 1344, 1157, 969, 787, 740 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.97 (d, *J*=8.2 Hz, 1H, ArH), 7.62–7.53 (m, 1H, ArH), 7.48–7.38 (m, 2H, ArH), 7.05–6.91 (m, 1H, =CH), 5.89 (dd, *J*=15.7, 9.0 Hz, 1H, =CH), 5.05–4.90 (m, 1H, C*H*HNO$_2$), 4.72 (dd, *J*=12.2, 5.8 Hz, 0.15H, C*H*HNO$_2$), 4.62 (dd, *J*=12.1, 9.2 Hz, 0.85H, C*H*HNO$_2$), 3.48–3.30 (m, 1H, CH), 2.48–2.01 (m, 5H, 5× C*H*H), 1.89–1.70 (m, 2H, 2× C*H*H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 219.2, 218.3, 147.4, 133.4, 132.4, 131.9, 130.6, 130.2, 129.4, 129.1, 128.6, 124.6, 77.6, 77.5, 50.3, 49.5, 42.6, 41.8, 39.1, 38.4, 27.4, 27.3, 20.8, 20.4; MS (ESI) *m*/*z* (%): 322 [M+NH$_4$, (100)]$^+$, 305 [M+H, (10)]$^+$; HRMS exact mass calculated for [M+H]$^+$ (C$_{15}$H$_{17}$N$_2$O$_5$) requires *m*/*z* 305.1132, found *m*/*z* 305.1124; HPLC analysis: 96:4 er, 85:15 dr; Diacel Chiralpak® AD-H column, hexane/2-propanol: 90:10, flow rate 1.0 mL/min, t_R=32.82 min (minor) and 45.30 min (major).

*4.4.14. (S)-2-[(S,E)-4-(4-Chlorophenyl)-1-nitrobut-3-en-2-yl]cyclopentanone (**3n**).*[10] Yellow oil (90%); $[\alpha]_D^{20}$ −19.3 (*c* 2.0, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.31–7.19 (m, 4H, ArH), 6.47 (d, *J*=15.8 Hz, 0.30H, =CH), 6.43 (d, *J*=15.8 Hz, 0.70H, =CH), 5.90 (dd, *J*=15.8, 9.5 Hz, 1H, =CH), 4.90 (dd, *J*=12.1, 5.5 Hz, 0.70H, C*H*HNO$_2$), 4.82 (dd, *J*=12.2, 8.8 Hz, 0.30H, C*H*HNO$_2$), 4.70 (dd, *J*=12.2, 6.1 Hz, 0.30H, C*H*HNO$_2$), 4.52 (dd, *J*=12.1, 9.2 Hz, 0.70H, C*H*HNO$_2$), 3.44–3.24 (m, 1H, CH), 2.42–1.98 (m, 5H, 5× C*H*H), 1.88–1.58 (m, 2H, 2× C*H*H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 219.0, 218.1, 134.5, 133.5, 128.7, 127.7, 127.6, 125.1, 124.4, 77.6, 50.2, 49.7, 42.6, 41.9, 39.1, 38.4, 27.4, 26.9, 20.7, 20.4; MS (ESI) *m*/*z* (%): 316 [M+Na, (60)]$^+$, 294 [M+H, (20)]$^+$; HPLC

analysis: 95:5 er, 70:30 dr; Diacel Chiralpak® AD-H column, hexane/2-propanol: 95:5, flow rate 1.0 mL/min, t_R=30.19 min (minor) and 38.76 min (major).

*4.4.15. (S)-2-[(S,E)-4-(4-Methoxyphenyl)-1-nitrobut-3-en-2-yl]cyclopentanone (**3o**).*[10] Yellow oil (83%); $[\alpha]_D^{20}$ −92.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.24 (d, *J*=8.8 Hz, 2H, ArH), 6.81 (d, *J*=8.8 Hz, 2H, ArH), 6.50–6.36 (m, 1H, =CH), 5.76 (dd, *J*=15.7, 9.2 Hz, 1H, =CH), 4.89 (dd, *J*=12.0, 5.8 Hz, 1H, C*H*HNO$_2$), 4.72 (dd, *J*=12.2, 6.4 Hz, 0.30H, C*H*HNO$_2$), 4.50 (dd, *J*=12.0, 9.1 Hz, 0.70H, C*H*HNO$_2$), 3.78 (s, 3H, OCH_3), 3.47–3.22 (m, 1H, CH), 2.46–1.97 (m, 5H, 5× C*H*H), 1.90–1.60 (m, 2H, 2× C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 219.5, 218.5, 159.4, 135.1, 134.0, 128.7, 127.7, 127.6, 121.9, 121.1, 113.9, 78.0, 77.9, 55.3, 50.1, 49.7, 42.8, 41.9, 39.3, 38.5, 27.4, 26.8, 20.8, 20.5; MS (ESI) *m*/*z* (%): 290 [M+H, (100)]$^+$; HPLC analysis: 94:6 er, 70:30 dr; Diacel Chiralpak® AD-H column, hexane/2-propanol: 90:10, flow rate 1.0 mL/min, t_R=27.08 min (minor) and 35.24 min (major).

*4.4.16. (S)-2-[(R,E)-3-Methyl-1-nitro-4-phenylbut-3-en-2-yl]cyclopentanone (**3p**).* Colorless oil (93%); $[\alpha]_D^{20}$ −82.1 (*c* 1.0, $CHCl_3$); IR (film) 2972, 2877, 1731, 1551, 1445, 1382, 1155, 1130, 920, 875, 749, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.12 (m, 5H, ArH), 6.36 (s, 1H, =CH), 5.36 (dd, *J*=12.0, 4.4 Hz, 1H, CHHNO$_2$), 4.93–4.80 (m, 0.20H, C*H*HNO$_2$), 4.65–4.48 (m, 0.80H, C*H*HNO$_2$), 3.48–3.35 (m, 0.20H, CH), 3.14–3.01 (m, 0.80H, CH), 2.47–2.26 (m, 2H, 2× C*H*H), 2.23–1.95 (m, 3H, 3× C*H*H), 1.87–1.55 (m, 5H, 2× C*H*H and CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 219.6, 218.5, 136.8, 136.7, 134.3, 132.9, 131.1, 129.8, 128.9, 128.1, 126.8, 126.7, 76.4, 76.1, 50.0, 49.2, 47.4, 47.2, 38.7, 28.8, 27.2, 20.5, 20.3, 16.2, 13.2; MS (ESI) *m*/*z* (%): 296 [M+Na, (75)]$^+$, 274 [M+H, (35)]$^+$; HRMS exact mass calculated for [M+H]$^+$ ($C_{16}H_{20}NO_3$) requires *m*/*z* 274.1438, found *m*/*z* 274.1430; HPLC analysis: 96.5:3.5 er, 80:20 dr; Diacel Chiralpak® OD-H column, hexane/2-propanol: 95:5, flow rate 0.8 mL/min, t_R=33.71 min (major) and 41.64 min (minor).

Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.07.078.

References and notes

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