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Diastereoselective 1,3-nitrooxygenation of bicyclo[1.1.0]butanes†

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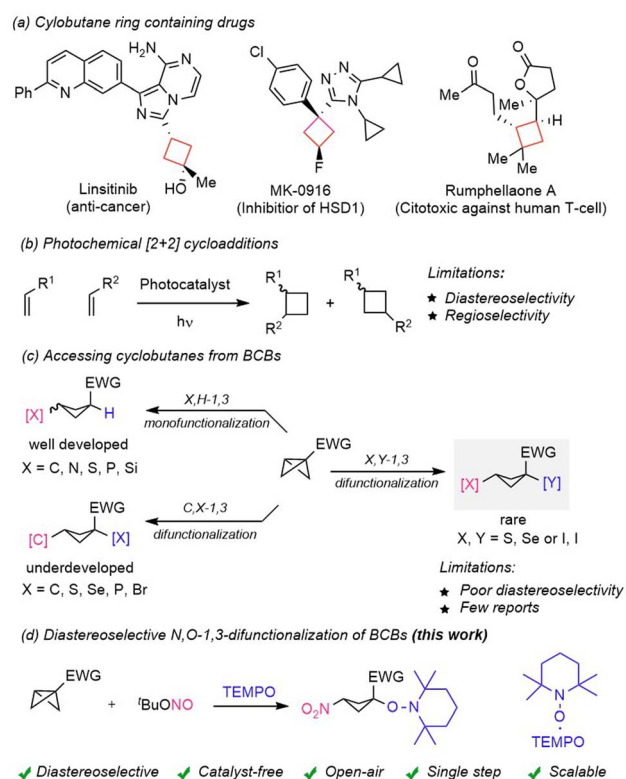
Cyclobutanes are strained carbocycles found in many drugs and natural products. Herein, we report a diastereoselective 1,3-nitrooxygenation of bicyclo[1.1.0]butanes with *tert*-butylnitrite and TEMPO to access 1,1,3-trisubstituted cyclobutanes. Various bicyclo[1.1.0]butanes effectively participated in the radical reaction yielding the substituted cyclobutane scaffolds with excellent yields and diastereoselectivity. The reaction is catalyst-free, easy to perform, and scalable and can be conducted in open air. Products obtained serve as substrates for the synthesis of 1,1,3,3-tetrasubstituted cyclobutanes with good yields and diastereoselectivity.

Introduction

Cyclobutanes are important structural units found in many naturally occurring and pharmaceutically active bio-molecules (Scheme 1a).¹ In this regard, nitrocyclobutanes^{1e,f} are highly valuable intermediates in organic synthesis^{1g} due to their unique dual reactivity, arising from both the strained cyclobutane core and the electron-withdrawing nitro group. The nitro functionality serves as a versatile handle for various transformations, including reductions to amines, Henry reactions, and Nef reactions, which facilitate the formation of ketones and other functional groups. More specifically, highly functionalized and well-decorated cyclobutanes are often challenging to synthesize in a straightforward manner. Major synthetic routes for the synthesis of these strained carbocycles include radical cyclization,² Wolff-rearrangement,³ oxidative pinacol-rearrangement,⁴ and the recently reported nitrogen-deletion strategy.⁵ Photocatalyst mediated intermolecular [2 + 2] cycloaddition⁶ has been extensively used for the construction of such strained carbocycles (Scheme 1b). However, despite significant advancement in energy transfer mediated photochemical [2 + 2] cycloadditions the outcome of these reactions is often complicated because of regio- and diastereoselectivity issues,⁶ and careful selection of π -systems is often a prerequisite criterion to achieve the desired selectivity. In recent years an additional approach has emerged, which involves the exploitation of strained bicyclo[1.1.0]butanes (BCBs)⁷ to access a variety of complex cyclobutane scaffolds (Scheme 1c). Due to the 96% p-character of the central C–C bond of a BCB, such compounds show a diverse range of reactivities varying from nucleophilic,

electrophilic and radicalophilic.⁷ The pioneering work of nucleophilic additions to BCBs was realized by Gaoni *et al.*⁸

Moreover, the Baran group⁹ developed amination of BCBs using amines as nucleophiles. Biju *et al.*¹⁰ and Feng, Qu, Yu *et al.*¹¹ independently developed diastereoselective arylation of



Scheme 1 (a) Cyclobutane ring containing drugs. (b) Photochemical [2 + 2] cycloaddition. (c) Accessing cyclobutanes from BCBs. (d) This work: diastereoselective *N,O*-1,3-difunctionalization of BCBs.

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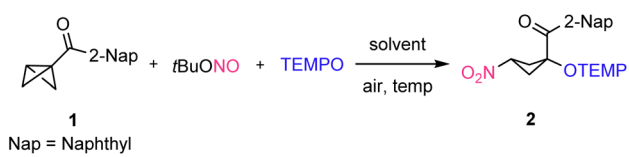
disubstituted-BCBs. Along with nucleophilic ring-openings, several radical additions^{1,12} to BCBs were reported, predominantly for mono-functionalization. Considering difunctionalizing ring-opening of BCBs, except for few cases, the majority of these transformations suffer from low diastereoselectivity. Along these lines, diastereoisomerically enriched 1,1,3-trisubstituted cyclobutanes were successfully prepared by the Fox group¹³ through organocuprate addition and subsequent trapping using an external electrophile. The Glorius group¹⁴ developed a 1,3-carbothiolation of BCBs through an intramolecular group transfer process to secure high *syn*-selectivity. The Hari group¹⁵ presented a 1,3-carboheterodifunctionalization of BCBs for the synthesis of spirocyclobutyl lactones and lactams, albeit with moderate diastereocontrol. Boronate-BCBs were investigated by the Aggarwal group¹⁶ who achieved highly diastereoselective 1,3-carbodifunctionalization by employing various electrophiles or electrophilic radicals to induce the ring-opening process. The preinstalled boronate functionality controls both regio- and diastereoselectivity of the products, 1,1,3-trisubstituted cyclobutanes.

In addition to mono and 1,3-difunctionalization, cycloaddition¹⁷ and insertion reactions¹ of BCBs have offered synthetic chemists direct and straightforward routes to access cyclobutane rings containing complex 3D-enriched scaffolds. However, only carbon–carbon (C–C) and carbon–heteroatom (C–S) 1,3-difunctionalization was presented in a diastereoselective manner to date. The diastereoselective heteroatom–heteroatom (X,Y) 1,3-difunctionalization of bicyclo[1.1.0]butanes is rare.¹⁸ In order to achieve a heteroatom–heteroatom, particularly (O–N) 1,3-difunctionalization, we considered using *tert*-butyl nitrite (^tBuONO)¹⁹ as a nitrogen atom source in combination with the TEMPO radical²⁰ as an oxygen atom source (Scheme 1d). ^tBuONO upon thermal homolysis will generate a persistent NO-radical, which in the presence of molecular oxygen will be oxidized to a transient NO₂-radical. The NO₂-radical should then add along the central C–C bond of the BCB to generate a transient adduct cyclobutyl radical, which can engage in a selective cross-coupling with the persistent TEMPO radical to afford the desired 1,3-difunctionalized cyclobutane product. Interestingly, in this reaction two persistent radicals (NO and TEMPO) are present and the persistent NO-radical is selectively converted to a transient NO₂-radical during the course of the reaction, while TEMPO remains unchanged. The suggested difunctionalizing BCB ring-opening reaction presents challenges that are product stability²¹ and diastereoselectivity control, as radical/radical cross couplings generally occur with very low barriers.

Results and discussion

Readily prepared (see the ESI[†]) bicyclo[1.1.0]butan-1-yl(naphthalen-2-yl)methanone (**1**) was chosen as the model substrate. We were pleased to observe that the reaction of **1** with ^tBuONO (0.20 mmol, 2.0 equiv.) and TEMPO (0.15 mmol, 1.5 equiv.) in DMSO at 70 °C for 18 hours afforded the desired 1,3-nitrooxygenated product **2** in 38% NMR-yield, albeit with a moderate 2.2 : 1 diastereoselectivity (Table 1, entry 1). Then,

Table 1 Reaction optimization



Chemical reaction scheme: **1** (bicyclo[1.1.0]butan-1-yl(naphthalen-2-yl)methanone) + ^tBuONO + TEMPO $\xrightarrow[\text{air, temp}]{\text{solvent}}$ **2** (1,3-nitrooxygenated product). Nap = Naphthyl.

#	Solvent	Temperature	dr	Yield ^{a,b} (%)
1	DMSO	70 °C	2.2 : 1	38
2	CHCl ₃	70 °C	1.4 : 1	82
3	DCE	70 °C	1.4 : 1	76
4	Toluene	70 °C	1.2 : 1	48
5	1,4-Dioxane	70 °C	1.1 : 1	64
6	CH ₃ CN	70 °C	1.0 : 1	74
7	CHCl ₃	25 °C	1.7 : 1	63
8	CHCl ₃	100 °C	3.9 : 1	81
9 ^c	CHCl ₃ (DMAP)	70 °C	4.4 : 1	82
10 ^c	CHCl ₃ (DBU)	70 °C	5.8 : 1	61
11 ^c	CHCl ₃ (Cs ₂ CO ₃)	70 °C	5.3 : 1	81
12	CHCl ₃	70 °C	>20 : 1	74 ^d

^a Reaction conditions: **1** (0.1 mmol), ^tBuONO (0.20 mmol), TEMPO (0.15 mmol), solvent (0.1 M), air, 18 h. ^b Determined by ¹H NMR using 1,3,5-trimethoxy benzene as an internal standard. ^c After removal of solvent the crude was re-dissolved in CHCl₃ (0.1 M) in the presence of the given base (20 mol%) and stirred for 18 h at rt. ^d Isolated yield and diastereomeric ratio after silica gel column chromatography of the reaction mixture.

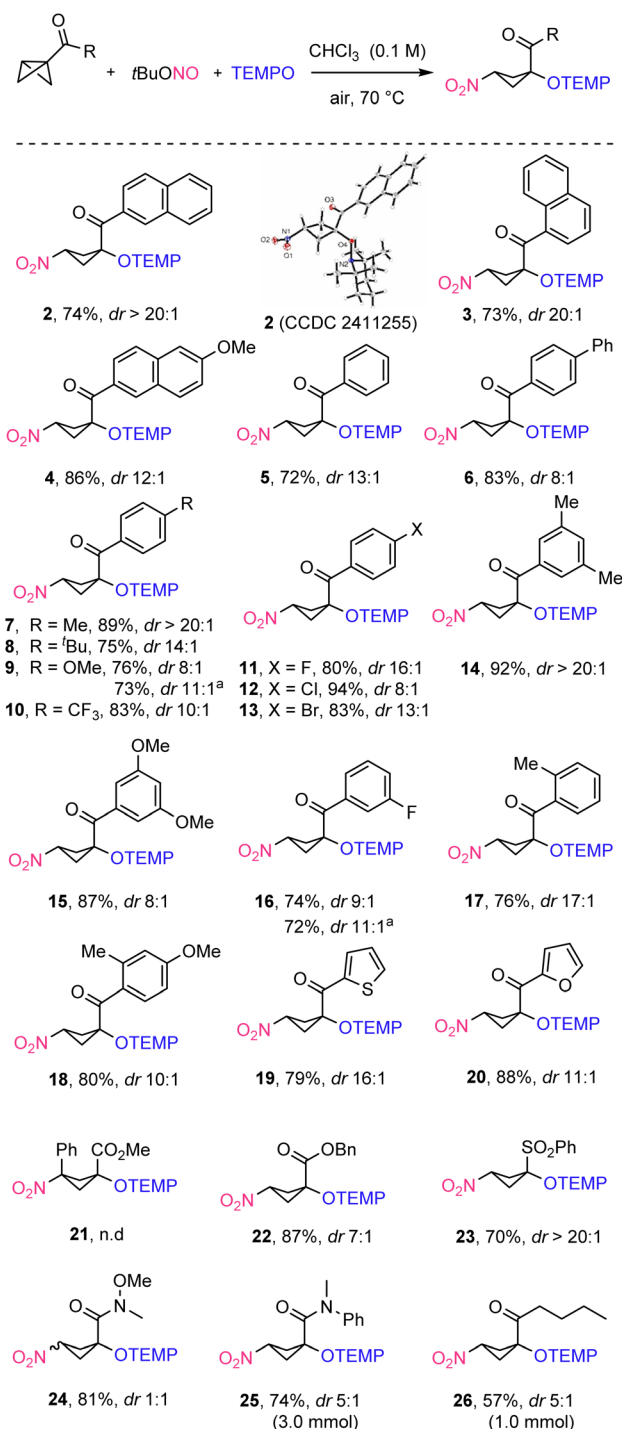
different solvents were tested under otherwise identical conditions. In CHCl₃, yield of the product **2** increased to 82% but diastereoselectivity further decreased (Table 1, entry 2). Other solvents such as DCE (76%), toluene (48%), 1,4-dioxane (64%), and CH₃CN (74%) afforded lower yields and lower diastereoselectivities (Table 1, entries 3–6). The lower efficiency of the transformation in toluene and 1,4-dioxane can be rationalized by considering the competitive hydrogen atom transfer (HAT) reaction with the reactive NO₂-radical from the solvent.

The optimization campaign was continued by varying reaction temperature using CHCl₃ as the solvent. At room temperature a significantly lower yield (63%) resulted, possibly due to the slow decomposition of ^tBuONO (Table 1, entry 7). Upon increasing temperature from 70 °C to 100 °C the yield of the reaction remained unchanged (81%); however, an improved diastereoselectivity was noted. This surprising stereochemical outcome indicated that isomerization likely occurred after initial BCB-nitrooxygenation, probably through deprotonation/re-protonation of the acidic proton next to the nitro group. Despite the fact that reversible alkoxyamine C–O-bond homolysis in **2** could not be excluded as the isomerization process at that temperature, we tested whether the poor diastereomeric ratio can be improved by applying a deprotonation/re-protonation strategy through simple addition of a base. To this end, several bases were tested as catalysts for the isomerization of **2**. After radical nitrooxygenation, the solvent was removed and the crude nitro-cyclobutane **2** was then re-dissolved in CHCl₃ in the presence of DMAP (20 mol%) and stirred for 18 h at room temperature. The diastereoselectivity



improved without compromising the yield (Table 1, entry 9, 82%, dr 4.4 : 1). With DBU (20 mol%) as the base, the diastereomeric ratio further improved, albeit at the expense of the NMR yield (Table 1, entry 10, 61%, dr 5.8 : 1). In the presence of Cs_2CO_3 (20 mol%), product 2 was obtained with a diastereomeric ratio of 5.3 : 1 without scarifying the yield (Table 1, entry 11). Pleasingly, upon purification of the crude product 2 through silica gel column chromatography without any prior base treatment, we found complete isomerization and 2 (*syn*-isomer) was isolated in 74% yield with an excellent diastereomeric ratio (dr > 20 : 1, Table 1, entry 12). The relative configuration was unambiguously assigned by X-ray analysis and other compounds prepared in this study were assigned in analogy. Obviously, the additional isomerization step using an external base is not required, as isomerization to the thermodynamic *syn*-product efficiently occurs during silica gel chromatography. With these optimized conditions in hand, we then investigated the scope of the reaction.

First, the aryl group of the keto BCB was varied. 1-Naphthyl and 6-methoxy-substituted 2-naphthyl-keto-BCBs afforded the desired products 3 and 4 in 73% and 86% yield with high diastereoselectivity (dr 20 : 1 and 12 : 1) (Scheme 2). The unsubstituted phenyl keto-BCB provided the desired cyclobutane 5 in 72% yield and high stereoselectivity (dr 13 : 1). Aryl keto-BCBs carrying an electron donating or withdrawing group at the aryl ring were eligible substrates. Thus, BCBs carrying an aryl group or an alkyl group at the 4-position of the aryl substituent such as 4-phenyl, 4-methyl, or 4-*tert*-butyl, afforded the desired products 6–8 with good to excellent yields (75–89%) and good to excellent diastereoselectivity (dr 8 : 1 to > 20 : 1). The reason for the varying selectivity as a function of the *para*-substituent is not fully understood. Along the same lines, electron-rich 4-MeOC₆H₄ and electron-poor 4-CF₃C₆H₄-substituted BCBs afforded the desired products 9 and 10 in 76% and 83% yield, with good diastereoselectivity (dr 8 : 1 and 10 : 1). Renewed chromatography of 9 led to a slightly improved diastereoselectivity (11 : 1 *versus* 8 : 1). 4-Halo-substituted aryl keto-BCBs delivered the targeted 1,3-nitrooxygated products 11–13 in good to excellent yields (80–94%) and good diastereoselectivity (dr 8 : 1 to 16 : 1). Installing a substituent at the *meta* position of the aryl ring such as in 3,5-dimethyl-C₆H₃, 3,5-dimethoxy-C₆H₃, and 3-fluoro-C₆H₄-substituted keto-BCBs afforded the desired products 14–16 in good to excellent yields (74–92%) and good to excellent diastereoselectivity (dr 8 : 1 to dr > 20 : 1). *ortho*-Methyl substituted phenyl keto-BCB delivered the 1,3-nitrooxygated product 17 in 76% yield with high diastereoselectivity (dr 17 : 1). A 2,4-disubstituted phenyl keto-BCB worked well to afford 18 in 80% yield with good diastereoselectivity (dr 10 : 1). Heterocyclic rings such as thiophene and furan are tolerated and the corresponding 1,3-nitrooxygated products 19 and 20 were isolated in 79% and 88% yields with high stereoselectivity (dr 16 : 1 and 11 : 1). However, a 1,3-disubstituted-BCB did not afford the desired 1,3-nitrooxygated product 21, possibly because of steric reasons: the 3-phenyl substituent in the BCB hinders NO₂-radical attack and ring opening does not occur.

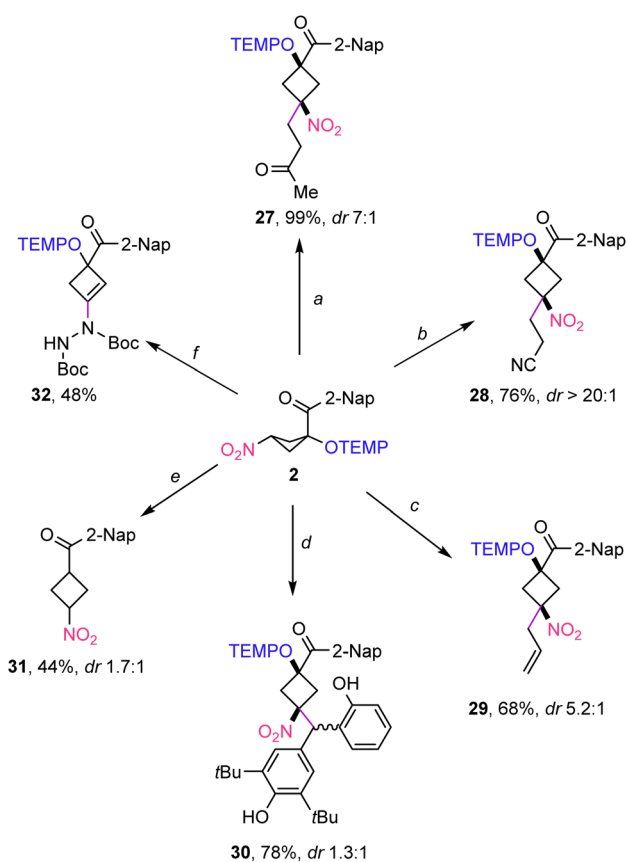


Scheme 2 Reaction conditions: bicyclo[1.1.0]butane (0.2 mmol, 1.0 equiv.), *t*BuONO (0.4 mmol, 2.0 equiv.), TEMPO (0.3 mmol, 1.5 equiv.), CHCl₃ (2.0 mL). Yields and the diastereomeric ratio are reported after isolation *via* column chromatography. ^aA second column chromatography was performed.

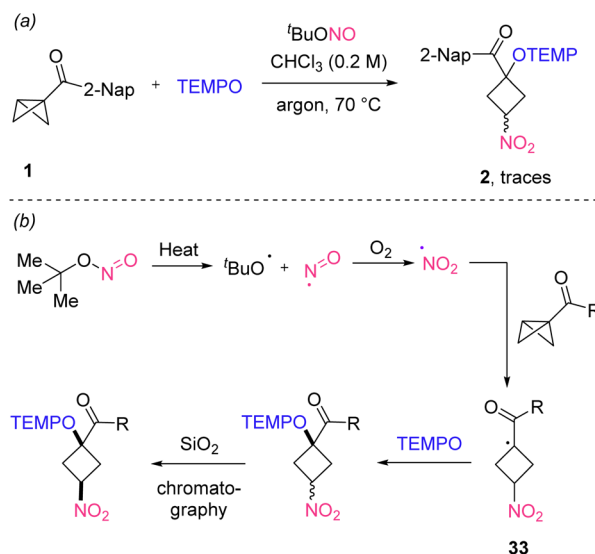
Moreover, phenylsulfonyl-activated BCBs also engage in the radical cascade reaction, as shown by the successful synthesis of sulfone 23 that was isolated in 70% yield with excellent diastereoselectivity (dr > 20 : 1). Notably, this methodology is not restricted to aromatic keto-BCBs. It is also effective for the ring-

opening di-functionalization of ester-BCBs, amide-BCBs, and alkyl keto-BCBs, yielding trisubstituted cyclobutane derivatives with good to excellent yields and low to moderate diastereoselectivity (**22**, 87%, dr 7 : 1; **24**, 81%, dr 1 : 1; **25**, 74%, dr 5 : 1; **26**, 57%, dr 5 : 1).

The synthetic value of the nitrocyclobutane products was documented by conducting several follow-up reactions (Scheme 3). Michael reaction of **2** with methyl acrylate and acrylonitrile afforded the 1,1,3,3-tetrasubstituted cyclobutanes **27** and **28** in 99% and 76% yields with good to excellent diastereoselectivity (dr 7 : 1 and dr > 20 : 1). Palladium catalysed allylation of **2** with allyl alcohol was achieved to afford **29** in 68% yield with moderate diastereoselectivity (dr 5.2 : 1). The relative configuration of the separable isomers was assigned by NOE experiments (see the ESI†). Selectivity of the other products derived from **2** was assigned in analogy. *para*-Quinomethide as



Scheme 3 Follow-up chemistry. ^aReaction conditions: **2** (0.15 mmol, 1.0 equiv.), methyl vinyl ketone (0.18 mmol, 1.2 equiv.), tetramethyl guanidine (0.075 mmol, 0.5 equiv.), THF (0.9 mL). ^bReaction conditions: **2** (0.15 mmol, 1.0 equiv.), acrylonitrile (0.18 mmol, 1.2 equiv.), tetramethyl guanidine (0.075 mmol, 0.5 equiv.), THF (0.9 mL). ^cReaction conditions: **2** (0.2 mmol, 1.0 equiv.), allyl alcohol (0.6 mmol, 3.0 equiv.), Pd(PPh₃)₄ (0.02 mmol, 0.1 equiv.), DMSO (1.2 mL). ^dReaction conditions: **2** (0.1 mmol, 1.0 equiv.), 2,6-di-*tert*-butyl-4-(2-hydroxybenzylidene)cyclohexa-2,5-dien-1-one (0.1 mmol, 1 equiv.), Cs₂CO₃ (0.11 mmol, 1.1 equiv.), Bi(OTf)₃ (0.02 mmol, 0.2 equiv.) DCE (1.0 mL). ^eReaction conditions: **2** (0.1 mmol, 1.0 equiv.), γ -terpene (0.3 mmol, 3.0 equiv.), *tert*-butanol (5.0 mL). ^fReaction conditions: **2** (0.10 mmol, 1.0 equiv.), di-*tert*-butyl (*E*)-diazene-1,2-dicarboxylate (0.15 mmol, 1.5 equiv.), Cs₂CO₃ (0.11 mmol, 1.1 equiv.), DCE (1.0 mL).



Scheme 4 (a) Control experiment. (b) Plausible reaction mechanism.

an electrophilic coupling partner delivered cyclobutane **30** in 78% yield, albeit with poor diastereoselectivity. Thermal homolysis of the weak C–O bond of alkoxyamine **2** in the presence of γ -terpene as a hydrogen atom transfer (HAT)²² reagent afforded the 1,3-disubstituted cyclobutane **31** in 44% yield (88%, brsm) and moderate diastereoselectivity. Hydrazination of nitrocyclobutane **2** under basic conditions gave cyclobutene **32** in 48% isolated yield. Hence, the targeted nitrocyclobutane obtained after initial hydrazination eliminates HNO₂ under the applied conditions.

In order to study the effect of O₂, the reaction of **1** was repeated under an argon atmosphere and only traces of product **2** were detected (Scheme 4a). Based on this observation and literature reports¹⁹ we propose a plausible mechanism that is depicted in Scheme 4b. Thermal homolysis of the N–O bond in *t*-BuONO leads to the formation of the *tert*-butoxyl radical along with the persistent nitroso (NO) radical, which in the presence of molecular oxygen is directly oxidized to the NO₂-radical. The NO₂-radical then engages in a homolytic substitution at carbon cleaving the central C–C bond of the bicyclo[1.1.0]butane to generate the adduct radical **33**. This adduct radical is then trapped by the persistent TEMPO radical²³ to deliver the isolated product. Of note, the TEMPO-trapping does not occur with a high stereoselectivity and isomerization through a deprotonation/re-protonation sequence forming a thermodynamically more stable isomer during silica gel chromatography and ensures the very high diastereoselectivity observed in many of our transformations.

Conclusions

In conclusion we have developed a highly diastereoselective 1,3-nitroxyoxygenation of bicyclo[1.1.0]butanes for the preparation of 1,1,3-trisubstituted cyclobutane scaffolds. It is shown that the radical ring-opening TEMPO-trapping occurs with low or moderate stereoselectivity. Nevertheless, due to the simple



isomerization through deprotonation/re-protonation during silica gel chromatography, the thermodynamic *syn*-isomer can be obtained with good to excellent diastereoselectivity. The reported cascade worked for a wide variety of substrates, delivering the targeted nitrocyclobutane products in good to very good yields. Follow-up chemistry demonstrated that the ring-opening products formed through the radical cascade can be used as substrates for the synthesis of 1,1,3,3-tetrasubstituted cyclobutane scaffolds with good diastereocontrol.

Data availability

Experimental procedures and analytical data (NMR, HRMS, IR, melting points) that support the findings of this study are available in the ESI.†

Author contributions

A. M. and K. B. conducted all the experiments and characterized all novel compounds. C. G. D. measured and solved the X-ray crystal structure. A. M., K. B. and A. S. designed the experiments and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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