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Organocatalytic intermolecular [2+2] cycloaddition of norbornadienes by a stable organic radical compound

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ABSTRACT

An organocatalytic [2+2] cycloaddition reaction of norbornadienes (NBDs) using catalytic amount of TEMPO was reported. Single crystal X-ray diffraction of the product revealed its detailed multicyclic structure containing a 4-membered ring, formed in intermolecular reaction. Addition of AIBN to the current catalytic system improved the product yield. Quantitative reaction of the NBD and TEMPO gave a 2:2 adduct of NBD and TEMPO, which was confirmed by HR-MS. This catalytic [2+2] addition of NBDs has great advantage in selective intermolecular coupling in comparison with [2+2] photocycloaddition.

Introduction

Cycloaddition is one of the most valuable reaction for construction of covalent organic frameworks. Especially to obtain a saturated 4-membered ring, [2+2] cycloaddition reaction of alkenes can be a powerful tool because of its wide range of applicable substrate, and high chemo- and stereoselectivity of the reaction.[1–6] The 4-membered ring can be found in some natural products, some of which are physiologically active.[7–9] There are examples using cyclobutane-containing compounds applied as a template for drug discovery research.[8,9] In the field of organic synthesis, the 4-membered framework is becoming more important, for instance, used as an intermediates for organic synthesis arranged by ring-opening and expansion reactions to afford cyclopentane or cyclohexane and even ring-contraction reactions to cyclopropane.[10]

Reported [2+2] cycloaddition of alkenes are generally classified into the following methods such as 1) light irradiation,[11,12] 2) transition metal-catalyzed reaction[13–19] and 3) Lewis acid-mediated reaction.[20–22] Each method has own distinctive advantages from the viewpoint of organic synthesis and thus is to be chosen according to desired products. This also means that developing a novel [2+2] cycloaddition system is of great importance to expand the frontiers of this field of chemistry and possibly to afford a new cyclobutane compounds.

Recently organocatalyst attracts much attention for green chemistry and distinctive catalytic acitivity.[23,24] As for alkene [2+2] cycloaddition, however, there has been no example promoted by organic radical catalyst, so far as we have known. In this paper, we displayed a new [2+2] cycloaddition system for alkenes using readily accessible 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as free radical catalyst. In the current work, norbornadiene (NBD) esters were applied as a starting olefinic substrate (Scheme 1) for an index for testing chemoselectivity among intra- or intermolecular [2+2] cycloaddition.

Results and discussion

An NBD ethyl ester, **1-Et**, dimerized in [2+2] cycloaddition manner in the presence of TEMPO to give pentacyclic product, **1-Et dimer** (Scheme 1). As in its NMR results, the obtained product included a mixture of stereoisomers of **1-Et dimer** (discussed below). Exact structure of one of the dimers was successfully displayed by single crystal X-ray analysis. The result was shown in Fig. 1. It clearly showed the presence of 4-membered ring at the center of the molecule. One of the two double bonds of **1-Et**, which is adjacent to ethyl ester group, participated in the reaction. In contrast, the other double bond of **1-Et** remained in unreacted form, confirmable at outside vinylene moieties of the product. Two ethyl ester groups were in vicinal to each other at endo-position toward norbornene backbone, bringing in C_2 symmetry on the molecule. Bicyclic diene like NBD can undergo *intra*molecular

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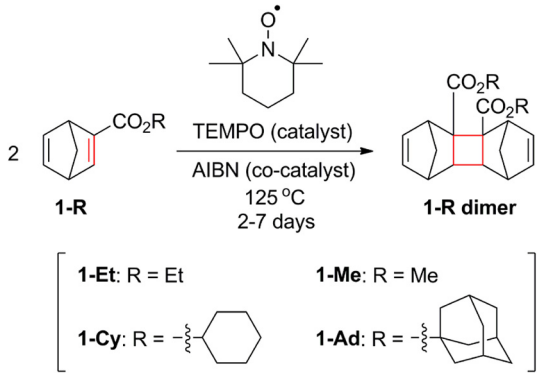

Scheme 1. Intermolecular [2+2] cycloaddition of NBD esters, **1-R**, catalyzed by TEMPO.

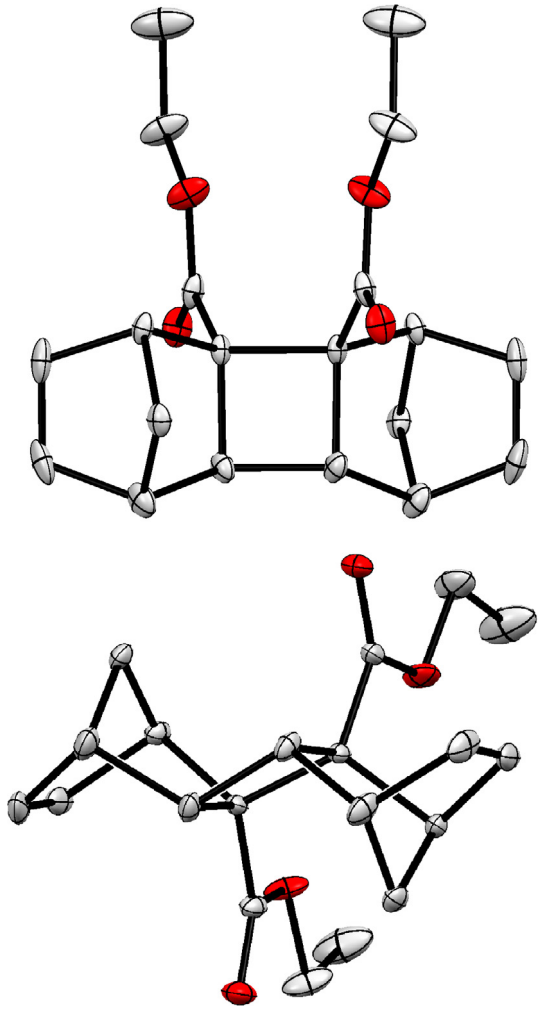

Fig. 1. Structures of **1-Et dimer** revealed by single crystal X-ray analysis (30% probability, red: oxygen atoms, gray: carbon atoms).[25]

[2+2] cyclization forming tetracyclic products in some case.[26,27] However, the current catalytic reaction with NBD ester selectively proceeds in *inter*molecular reaction forming its dimer. HR-MS result confirmed the dimerization reaction of **1-Et**.

It is noted that the product yield of **1-Et dimer** was improved with using 2,2′-azobis(2-methylpropionitrile) (AIBN) along with TEMPO (Table 1, entry 2). Although using solvents such as anisole or DMSO did not prevent the reaction (entries 3 and 4), higher yield of product was provided under solvent-free condition (entry 2). The best yield was given under the condition with binary catalyst composed of TEMPO and AIBN for longer reaction time of 7 days (entry 5).

Table 1
Results of organocatalytic [2+2] cycloaddition of NBD esters, **1-R**.[a]

Entry	Substrate	Time (hours)	Solvent	Catalyst(s)		Yield (%)[b]
				AIBN (mol%)	TEMPO (mol%)	
1	**1-Et**	48	none	0	5	57
2		48	none	2	5	62
3		48	anisole	2	5	42
4		48	DMSO	2	5	31
5		168	none	2	5	76
6	**1-Me**	48	anisole	2	5	39
7		168	none	2	5	64
8	**1-Ad**	48	anisole	2	5	0
9		168	none	2	5	trace
10	**1-Cy**	168	none	2	5	32

[a] At 125 °C.
[b] Determined by ^{1}H NMR.

Fig. 2 shows ^{1}H NMR spectra of reaction substrate **1-Et** [Fig. 2(a)] and a mixture of isolated stereoisomers of **1-Et dimers** obtained in entry 5 [Fig. 2(b)]. The product shows multiple pair of peaks in the unsaturated region in around 5.8–6.4 ppm, which are assignable to vinylene protons at g and h position of the [2+2] cyclic adduct. The observed peaks specifically in this olefinic region indicate that this reaction produces a mixture of regio/stereoisomers including the confirmed one by X-ray analysis.

Other NBD esters bearing sterically smaller or larger substituents were applied in the current catalytic system. In the case of **1-Me** and **1-Cy**, the [2+2] cycloaddition successfully proceeded under the condition optimized for **1-Et**, although product yields did not reached to that in the case of **1-Et**. Bulkier **1-Ad** barely gave [2+2] cycloaddition product, which is assumingly due to the steric hindrance of the substituent for [2+2] cyclization. Unfortunately, the current [2+2] reaction catalyzed by TEMPO did not proceed in the case of alkene compounds such as 2,5-norbornadiene, 2,3-dimethoxycarbonyl-2,5-norbornadiene, ethyl acrylate, methyl methacrylate, coumarin, and stilbene.

To understand reaction mechanism, we attempted to capture reaction intermediates of the current reaction. With large excess of catalysts such as 50 mol% TEMPO and 25 mol% AIBN, **1-Et** reacted to form the **1-Et dimers** along with another products which were detected by HR-MS. The result displayed a peak of m/z = 641.4525, corresponding to the adduct composed of 2 molecules of **1-Et** and 2 molecules of TEMPO. It suggests the formation of precursor of [2+2] cyclic adduct such as shown in Scheme 2. According to several reports treating polymerization of NBD esters,[28–31] radical species react with NBD esters to form a new radical species having norbornene backbone **2-R** (Scheme 3). Although the radical intermediate **2-R** initiates polymerization of NBD esters when using AIBN alone, the current system with TEMPO/AIBN seemingly did not favoured sequential reaction such as polymerization. In the reaction of **1-Et** with TEMPO, intermediate **2-TEMPO** possibly dimerizes to form another intermediate **3**, which corresponds to the HR-MS result shown above. Relatively weak C—O bond between an NBD framework and a TEMPO moiety reversibly dissociates and re-forms TEMPO molecules along with concerted formation of 4-membered ring.

As shown above, addition of AIBN as co-catalyst to TEMPO improved the product yield as compared to the case with lone TEMPO catalyst. AIBN itself can be a polymerization initiator for