Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

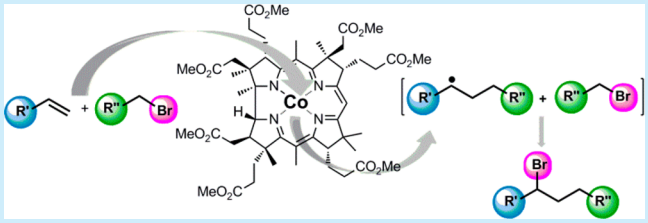
Vitamin B_{12} Catalyzed Atom Transfer Radical Addition

Keith ó Proinsias,* Agnieszka Jackowska, Katarzyna Radzewicz, Maciej Giedyk, and Dorota Gryko*

Institute of Organic Chemistry PAS, Kasprzaka 44/52, 01-224 Warsaw, Poland

Supporting Information

ABSTRACT: Vitamin B_{12}, a natural Co-complex, catalyzes atom transfer radical addition (ATRA) of organic halides to olefins. The established conditions were found to be very selective, with atom transfer radical polymerization (ATRP) occurring only in the case of acrylates.



Vitamin B_{12} (cobalamin, B_{12}, **1**, Figure 1) is a highly functionalized, benign molecule with a very unique and

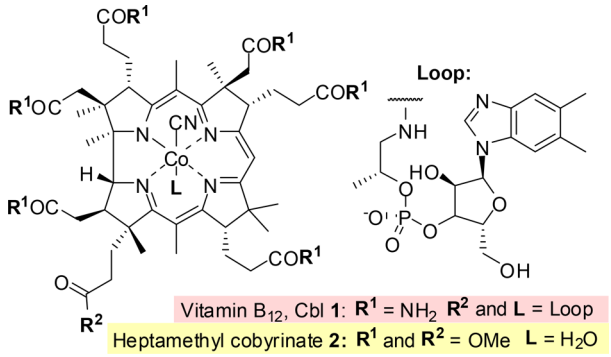


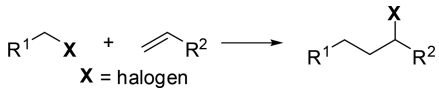
Figure 1. Vitamin B_{12} **1** and heptamethyl cobyrinate $(CN)(H_2O)$-Cby$(OMe)_7$ **2**.

stable cobalt center.[1] Upon reduction of cobalamin or its derivatives, either radical Co(II) or supernucleophilic Co(I) species is formed, which upon reacting with radicals or electrophiles ultimately leads to alkyl cobalamins.[2] Typically, B_{12}-catalyzed reactions adhere to a radical mechanism and numerous chemical transformations have been developed in this area, evolving B_{12}-catalysis beyond its natural coenzyme functions (homocoupling, methylation, isomerization, etc.).[1−3] But intermolecular reactions involving organic halides have been rather limited due to undesirable side reactions, i.e. dehalogenation and homocoupling, taking precedence.[2,4]

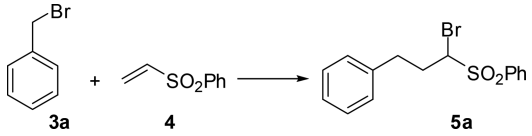
Since its discovery in 1937 by Kharasch, atom transfer radical addition (ATRA, Scheme 1) has made considerable advances developing into a unique and highly desirable method of generating carbon−carbon and carbon−halogen bonds in a single reaction system.[5] Unfortunately, the majority of these approaches require high metal-catalyst loading (10−30 mol % in relation to the alkene) to achieve high selectivity and the need for reagents such as peroxides, organotin reagents, and triethyl boron, as well as harsh reaction conditions, e.g. high temperature.[6] Other commonly used reagents include $TiCl_3$, copper, iron bimetallic Rh−Ru complexes, and chromium(II) acetate, to name a few.[7] On the other hand, Melchiorre et al. demonstrated that by using only *p*-anisaldehyde (20 mol %) in the presence of 2,6-lutidine and light, it is possible to perform selective intermolecular ATRA reactions of primarily bromo-malonate and -propanate type haloalkanes with aliphatic olefins.[8]

To date, cobalt complexes are often applied as catalysts in atom transfer radical polymerization (ATRP) reactions. In contrast, selective Co-catalyzed ATRA reactions, to the best of our knowledge, are unexplored.[9] We envisaged that vitamin B_{12}, a benign cobalt complex, might be a suitable catalyst for this process. This concept holds a multitude of challenges, with the obvious concern being that the preferred route for B_{12}-catalyzed reactions involving organic halides is dehalogenation.

Scheme 1. Atom Transfer Radical Addition (ATRA)



Scheme 2. Model Reaction of Benzyl Bromide (3a) with Phenyl Vinyl Sulfone (4)

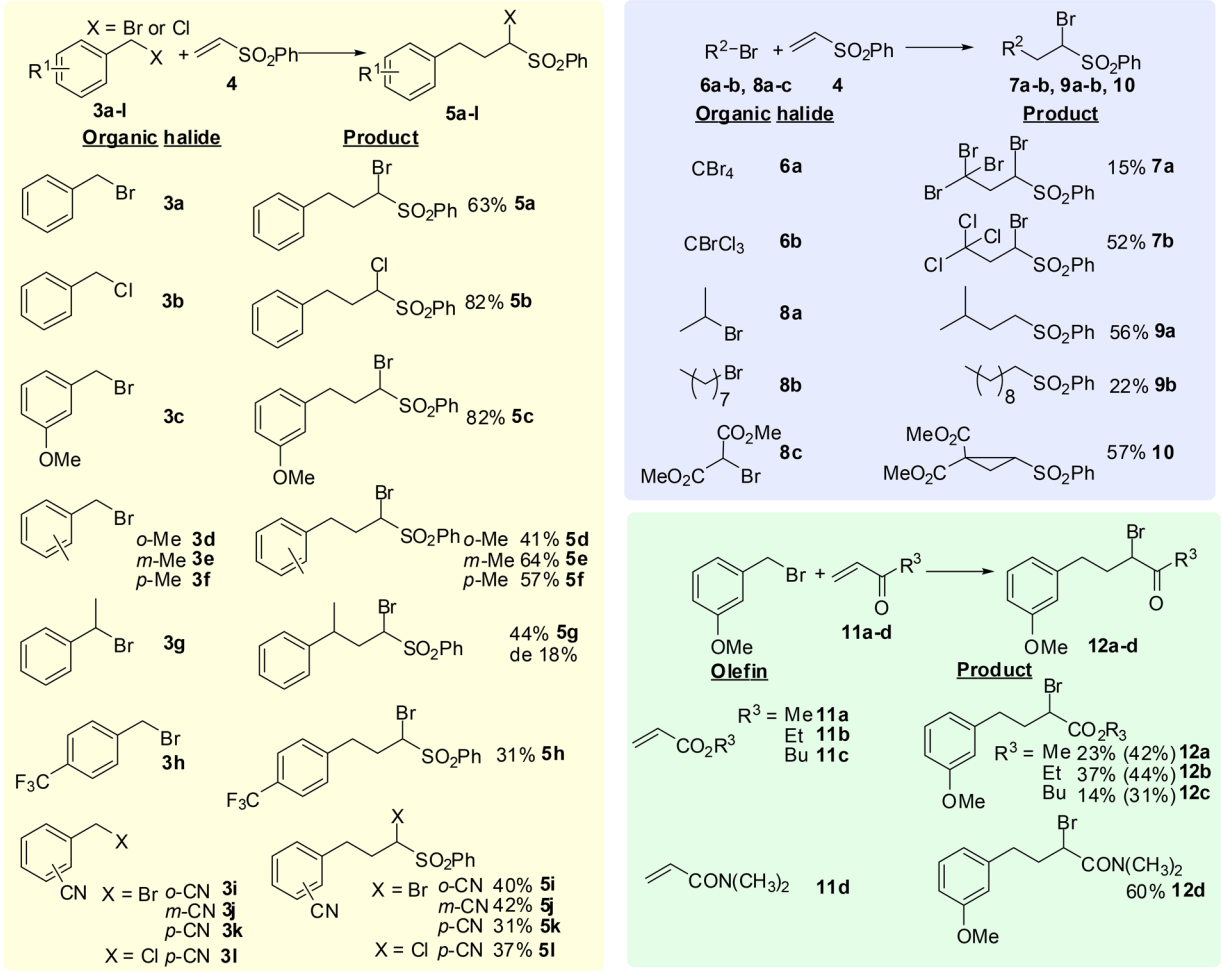


The initial exploratory experiments showed that ATRA only occurs if the reaction is conducted in a microwave reactor[10] using either THF or toluene as a solvent, and $NaBH_4$ as a reducing agent preferably over the more commonly used zinc for the efficient reduction of the catalyst.[2] Heptamethyl cobyrinate[11] (**2**, Figure 1) was the catalyst of choice for this

Received: November 29, 2017

DOI: 10.1021/acs.orglett.7b03699
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Scope and Limitation Studies[a]



[a]Conditions: organic halide (0.84 mmol), olefin (0.28 mmol), (CN)(H$_2$O)Cby(OMe)$_7$ (**2**, 27 mg, 0.025 mmol, 8 mol %), NaBH$_4$ (20 mg, 0.5 mmol), Cs$_2$CO$_3$ (85 mg, 0.26 mmol), toluene (0.5 mL), 90 °C MW 300 W, 40 min. Conditions for acrylates **11a–c**: *m*-methoxybenzyl bromide (**6a**, 35 μL, 0.28 mmol), acrylate (0.28 mmol), (CN)(H$_2$O)Cby(OMe)$_7$ (**2**, 27 mg, 0.025 mmol, 8 mol %), NaBH$_4$ (19 mg, 0.5 mmol), Et$_3$N (36 μL, 0.25 mmol), toluene (0.5 mL), 90 °C MW 300 W, 40 min.

reaction. *The catalyst was recovered, purified, and reused post-reaction* (see Supporting Information (SI) for full optimization tables). The reaction of benzyl bromide (**3a**) with phenyl vinyl sulfone (**4**) was used in the optimization studies (Scheme 2). The use of 3 equiv of benzyl bromide (**3a**) and 8 mol % of catalyst **2** allowed isolation of product **5a** in 63% yield (Table 1, entry 1). By decreasing the catalytic loading, using a higher concentration of benzyl bromide (**3a**), or extending the reaction time, a drop in yield was observed (entries 2–5), but importantly in all cases ATRP or dehalogenation of the product was not observed. With the optimal conditions in hand, scope and limitation studies were undertaken (Scheme 3). Interestingly, replacing benzyl bromide (**3a**) with benzyl chloride (**3b**) gave a sharp increase in the yield, giving compound **5b** in 82% yield. High yielding reactions were also observed for 3-methoxybenzyl bromide (**3c**) and *m*-methyl-benzyl bromide (**3e**). Expectedly, substrates possessing electron-withdrawing groups (**3h–l**) gave products **5h–l** in only moderate yields (31–42%).

In the case of *p*-cyanobenzyl chloride (**3l**) an increase in the yield, which occurred for substrate **3b**, was not observed. Furthermore, reactions with organic halides typically used in ATRAs, CBr$_4$ (**6a**), and CBrCl$_3$ (**6b**), afforded compounds **7a** and **7b** in 15% and 52% yield, respectively. Notably, all reactions proceeded considerably cleanly, lacking the expected array of byproducts caused by dehalogenation of either a substrate or a product. In the case of (1-bromoethyl)-benzene (**3g**) only a slight decrease in the yield was found giving compound **5g** in 44% yield (18% d.e.). Isopropyl- (**8a**) or octyl- (**8b**) bromides afforded products **9a** and **9b** in moderate

Table 1. Optimization Studies of ATRA Reaction[a]

entry	**3a** (mmol)	**2** (mol %)	time (min)	yield of **5** (%)
1	0.8	8	40	63
2	0.8	4	40	52
3	0.8	8	60	44
4	1.2	8	40	44
5	1.2	8	60	40
6	0.8	4	60	55
7	0.8	3	40	57
8	0.8	2	40	57

[a]Conditions: benzyl bromide (**3a**), phenyl vinyl sulfone (**4**) (47 mg, 0.28 mmol), (CN)(H$_2$O)Cby(OMe)$_7$ (**2**, 27 mg, 0.025 mmol, 8 mol %), NaBH$_4$ (20 mg, 0.5 mmol), Cs$_2$CO$_3$ (85 mg, 0.26 mmol), toluene (0.5 mL), 90 °C MW 300 W, 40 min.

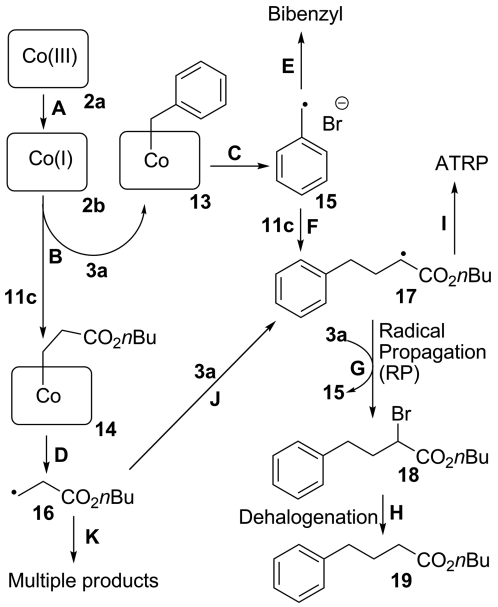
DOI: 10.1021/acs.orglett.7b03699
Org. Lett. XXXX, XXX, XXX–XXX

yields bereft of the bromide substituent, presumably due to either the Michael addition occurring or instant dehalogenation of the ATRA product. In the case of dimethyl bromomalonate (**8c**) unprecedented cyclopropanation was observed, even though such a starting material is common in ATRA studies. Cyclopropane **10** was isolated in 57% yield. In this case, the presence of a base (Cs_2CO_3) might deprotonate the ATRA product (traces of which were detected) consequently inducing cyclization. Acrylates with α- or β-methyl substituents failed to give desired products. This was also true for halobenzenes and (2-bromoethyl)benzene.

Acrylates (**11a−c**) posed much more of a challenge, due to polymerization or other side reactions occurring, mainly ATRP, which viciously affected the yield. Consequently, an excess of an acrylate must be used. In the case of methyl (**11a**) and *n*-butyl acrylate (**11c**) the yield increased 2-fold to 42% and 31% respectively. Interestingly, polymerization was not an issue when using acrylamide (**11d**) that gave product **12d** in 60% yield. (See SI for a full listing of the scope study.)

The proposed mechanism is presented in Scheme 4. The reduction of catalyst **2a** (Co(III)) gave supernucleophilic

Scheme 4. Plausible Mechanism for the Vitamin B_{12} Catalyzed ATRA Reaction



Co(I) **2b** (**A**), which upon reacting with benzyl bromide **3a** gave β-methyl substituted acrylates which failed to give the desired products. This was also true for halobenzenes and (2-bromoethyl)benzene cobalt complexes **13** (ESI-MS $[M]^+$ 1127 and $[M + CN]^+$ 1153) and **14** (ESI-MS $[M + CN + Na]^+$ 1215) (**B**). Following the homolytic cleavage radicals **15** (**C**) and **16** (**D**) are liberated. This was further confirmed via the addition of TEMPO, a radical trapping reagent, into the reaction mixture, which halted the reaction confirming a radical based reaction. Benzyl radical **15** then reacts with *n*-butyl acrylate (**11c**) to give intermediate **17** (**F**), which was also trapped with TEMPO (ESI-MS $[M + Na]^+$ 398). Radical **15** can also undergo homocoupling, giving bibenzyl (**E**). In our opinion, the mechanism adheres to a typical radical propagation pathway (**G**), in which a second molecule of benzyl bromide (**3a**) reacts with radical **17** forming desired product **18** and benzyl radical **15**. Alternatively, acrylate radical **16** can react with benzyl bromide **3a** to also give intermediate **17** (**J**), which ultimately leads to product **18** or undergo polymerization as well as other side reactions (**K**).

We have developed, to the best of our knowledge, the first example of the selective cobalt-catalyzed ATRA reaction with more common ATRP processes being suppressed. The reaction is catalyzed by hydrophobic vitamin B_{12}, a corrin cobalt complex, giving products in decent yields. Benzyl bromides and chlorides bearing electron-donating groups furnished products in higher yields than those with electron-withdrawing ones. Interestingly, utilization of aliphatic organic halides led to products bereft of the halogen substituent, while for dimethyl bromomalonate (8c) cyclopropane **10** formed instead.

We assume that the reaction proceeds through a radical mechanism involving dehalogenation of an organic halide by the catalyst **2**, followed by addition to an olefin followed by the typical radical propagation.

This work displays vitamin B_{12} catalysis in a new light, in terms of its relationship with organic halides. By fine-tuning the reaction conditions, one can embrace the uniqueness of this catalyst and expand its application beyond known biochemical processes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03699.

Experimental procedures, optimization studies, ^1H and ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: dorot.gryko@icho.edu.pl.
*E-mail: keithoproinsias@gmail.

ORCID

Dorota Gryko: 0000-0002-5197-4222

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by the National Science Centre (grant: SONATA 2013/11/D/T5/02956 and OPUS no. 2016/21/B/ST5/03169).

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Org. Lett. XXXX, XXX, XXX−XXX