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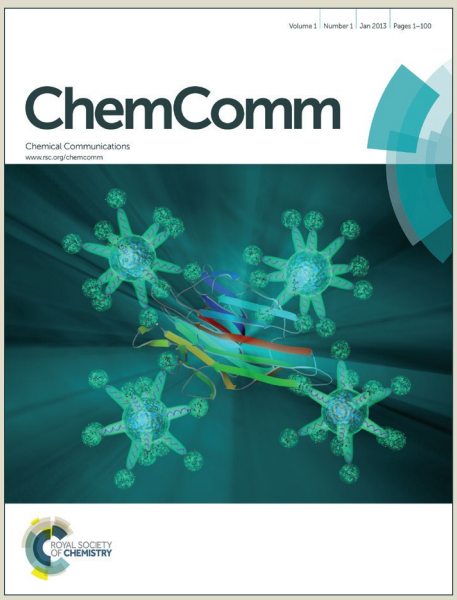

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Cobalt(I)-catalysed CH-alkylation of terminal olefins, and beyond

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Cobalester, a natural nontoxic vitamin B_{12} derivative was found to catalyse unusual olefinic sp^2 C-H alkylation with diazo reagents as a carbene source instead of the expected cyclopropanation.

Diazocarbonyl compounds are important and useful reagents in organic chemistry due to their ease of integration into numerous chemical transformations under mild conditions.[1] Particularly, they are utilised in cyclopropanation, direct insertion into sp^3 C-H, aromatic sp^2 C-H, and sp C-H bonds as well as heteroatom-H bonds.[2-7] Until recently, C-H functionalisation was mainly achieved with Rh and Cu catalysts,[1d] as well as other group 11 metals.[8] Nowadays, methodologies avoiding the use of harmful and toxic reagents have attracted a lot of attention with Fe,[9] Co,[10] and Cr[11] being recognised as valuable catalysts.

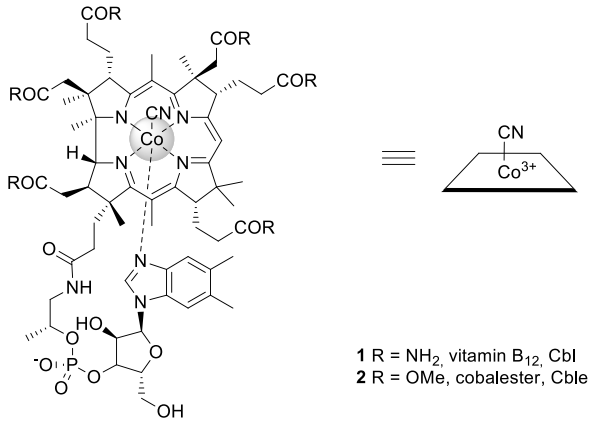
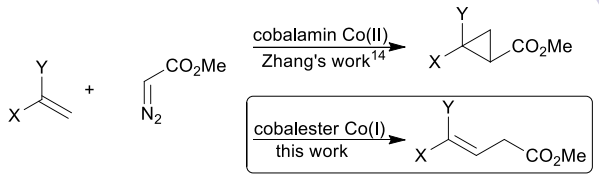


Fig. 1 Structure of vitamin B_{12} and cobalester.

In this regard, vitamin B_{12} (**1**, CbI, cobalamin, Fig. 1), being a natural, environmentally benign Co-complex bears advantages over other transition metal compounds. Its catalytic properties are inherently connected with the ability to form alkyl derivatives via Co(II) and Co(I) reduced forms.[12] To date, 'supernucleophilicity' of the Co(I) species (B_{12}s) and radical character of the Co(II) form (B_{12}r) have been investigated in numerous chemical reactions, such as dehalogenation, additions to activated alkenes, functional group migration, dimerisation, cyclopropanation and cyclopropane ring opening.[13] In 2004 Chen and Zhang reported that the reaction of styrenes with ethyl diazoacetate (EDA) in the presence of (HO)CbI led to cyclopropane derivatives (Scheme 1).[14]



Scheme 1 Functionalisation of olefins with EDA.

Their proposed mechanism suggests that the reaction involves the formation of Co(II) species that when reacted with EDA generates C-centred alkylcobalamin radical. On the other hand, carbene complexes, formed via reaction of diazo compounds with metal salts, including cobalt, are known to trap nucleophiles and insert into C–H bonds.[1a] On this basis *we questioned whether and how diazo reagents, those of electrophilic character, would react with 'supernucleophilic' B_{12}s*. We presumed that the reaction should provide alkylcobalamins that upon heating or light irradiation would generate radicals that could either disproportionate, abstract $H^{\cdot}$, or self-couple.

Our recent investigations into vitamin B_{12}-catalysed dimerisation of benzyl bromides led us to use newly developed cobalester (**2**, CbIe(III)) as a catalyst for the designed reaction.[15] Firstly, EDA was reacted with cobalester **2** in the presence of a reducing system (Zn/NH_4Cl) to prove the formation of hypothesised alkylcobalamin. Indeed, mass spectrometry analysis (ESI MS) of the reaction mixture showed a peak at 1506.8 corresponding to the desired alkylcobalester (see ESI). Following this observation, EDA was reacted with 1,1-diphenylethene (**3**) in the presence of CbIe (**2**) under light irradiation (Scheme 3, Table 1, entry 3). A mixture of two compounds formed; product **4a** and ester **5a** with the reduced

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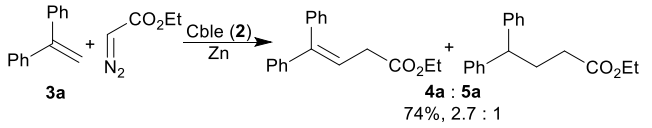
double bond. Surprisingly, ^{1}H NMR analysis revealed no evidence of cyclopropanation occurring.



Scheme 2 Cble-catalysed reaction of 1,1-diphenylethene (**3a**) with EDA: 1,1-diphenylethene (**3a**, 0.5 mmol), EDA (3 equiv.), Cble (**2,** 1 mol%), Zn (3 equiv.), NH_4Cl (3.4 equiv.), MeCN (2.5 mL), LED light, 18 h.

So far, the only examples representing functionalisation of double bonds are reactions of enones with diazocompounds reported by Ryu et al.,[16] Noels,[17] and Maruoka,[18] and that of α,β-unsaturated oximes leading to pyridine *N*-oxides.[6e] Our reaction represents the first example of alkylation of electron-rich double bonds with diazo reagents affording Heck-type products.

Subsequently, we systematically preformed optimisation of the reaction conditions with regard to solvent, catalyst loading, Zn, NH_4Cl, and time to favourably form the Heck-product. Among solvents allowing for the reduction of catalyst **2**, MeCN was found to be the solvent of choice (see ESI). Control experiments revealed that in the absence of light, at room temperature the extrusion of nitrogen from the reaction slowed and products **4a** and **5a** (1.4 : 1) formed in only 34% combined yield (Table 1, entry 1). An increase in the reaction's temperature to 42 ˚C (equivalent to photoreactor) improved the yield but decreased the selectivity (entry 4). Generally, photocatalytic reactions assured better selectivity (entries 2, 3), hence reactions were performed under light irradiation.

Table 1 Optimisation: the influence of light and temperature.[a]

Entry	Light	T [°C]	Conversion [%]	Yield [%]	4a : 5a ratio
1	-	RT	63	34	1.4 : 1
2	LED	15	78	28	2.6 : 1
3	LED	-	94	74	2.7 : 1
4	-	42	94	65	1.3 : 1
5	-	60	86	68	1.5 : 1

[a]Reaction conditions: 1,1-diphenylethene (0.5 mmol), EDA (3 equiv.), Zn (3 equiv.), NH_4Cl (3.4 equiv.), Cble **2** (1 mol%), MeCN (2.5 mL), 18 h.

The product ratio strongly depended on the amount of Zn and NH_4Cl used (Table 2). Almost in all cases yields remained high while the selectivity increased with an increase in Zn amount and with a decrease in the amount of NH_4Cl reaching a **4a** : **5a** ratio of 13 : 1 (Table 2, compare entries 1 to 3 and 3 to 4).

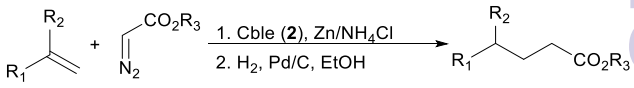
Table 2 Optimisation: the influence of zinc and ammonium chloride.[a]

Entry	Cble 2 [mol%]	Zn [equiv.]	NH_4Cl [equiv.]	Yield [%]	4a : 5a ratio
1	1	3	3.4	74	2.7:1
2	5	3	3.4	91	6 : 1
3	2	6	3.4	91	5 : 1
4	2	6	1.1	79	13 : 1

[a]Reaction conditions: 1,1-diphenylethene (0.5 mmol), EDA (3 equiv.), Zn, NH_4Cl, Cble **2** (2 mol%), MeCN (5 mL), 18 h light: 2x300 Lm LED warm light

Having established effective reaction conditions (Table 1, entry 3) we next focused on examining the scope of various compounds with terminal double bonds (Table 3).

Table 3 Substrate scope of C-H functionalisation of olefins.[a]

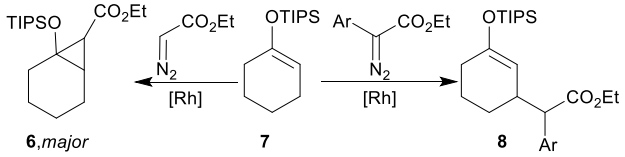


Entry	R_1	R_2	R_3	t [h]	5	Yield [%]
1	Ph	Ph	Et	18	**a**	91
2	Ph	Ph	*t*-Bu	18	**b**	67
3	Ph	Ph	$(CH_2)_3Ph$	18	**c**	60
4[b]	Ph	Ph	CH_2Ph	18	**d**	71[b]
5	Ph	$CH_2C(CH_3)_2Ph$	Et	18	**e**	57
6	Ph	H	Et	6	**f**	44
7	4-FC_6H_4	H	Et	6	**g**	1
8	4-ClC_6H_4	H	Et	6	**h**	22[c]
9	4-BrC_6H_4	H	Et	6	**i**	2
10	4-$MeOC_6H_4$	H	Et	6	**j**	38
11	3-$MeOC_6H_4$	H	Et	6	**k**	23
12	2-$MeOC_6H_4$	H	Et	6	**l**	18
13	4-$CO_2MeC_6H_4$	H	Et	6	**m**	0
14	-$CH_2CH_2CH_2CH_2$-		Et	18	**n**	73
15[d]	C_6H_4-2-Me	C_6H_4-2-Me	Et	18	**o**	68[d]

[a]Reaction conditions: alkene (**3**, 0.5 mmol), EDA (3 equiv.), Cble (**2**) (2 mol%), [illegible] (6 equiv.), NH_4Cl (3.4 equiv.) MeCN (5 mL), light. [b]Benzyl moiety was cleaved during hydrogenation step, giving 4,4-diphenylbutanoic acid **5d** as a product. [c]Product **5f** was isolated instead of expected halogenated compounds. [d]Subsequent hydrogenation was not performed as only unsaturated product was formed in the reaction

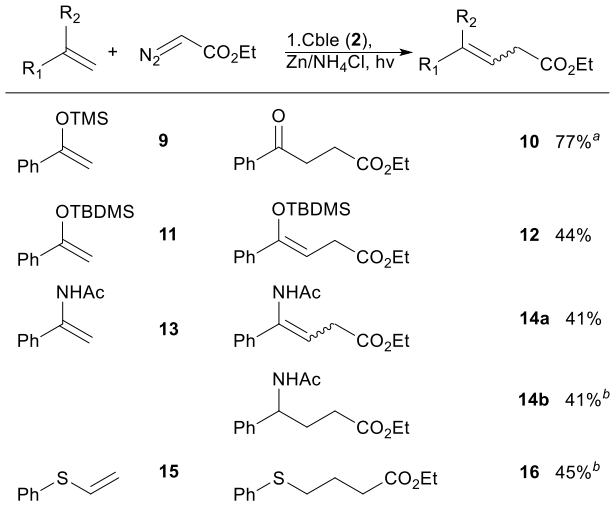
As the scope of the study focused on overall yield, the subsequent hydrogenation was performed exclusively furnishing the saturated product **5**. In styrene series **3f-l** (entries 6-13) only electron rich substrates **3f**, **3j-l** were reactive enough to furnish 1,2-disubstituted olefins as a mixture of *trans*- and *cis*-diastereoisomers. These results are in contrast to Hwang and Ryu work reporting sp^2 C-H bond functionalisation of only electron-deficient olefins - cyclic enones.[16] In the case of halogenated styrene derivatives, all except the fluorinated one underwent dehalogenation giving compound **5f** in low yield (entry 8-9). It is worth to note that in all cases cyclopropanation was not observed. Furthermore, an efficient reaction took place for methylenecyclopentane (**3n**, entry 10) and 1-methyl-2-[1-(2-methylphenyl)vinyl]-benzene (**3o**, entry 15), with no saturation being detected. Presumably, once product **5o** is formed, the sterically hindered double bond has a limited access to the cobalt centre. As far as diazocompounds are concerned only monosubstituted derivatives furnished desired products. Furthermore, we envisaged that this approach demonstrated the potential for targeting electron rich double bonds such as those present in enol ethers, enamides, or vinyl sulfides. Enol ethers were examined by Davies and Ren, however only functionalisation at the allylic position with aryldiazoacetates was reported, while EDA predominantly afforded cyclopropanation products (Scheme 3).[19] Later, they were found to react with

aryldiazoacetates in the presence $Rh(OAc)_4$ to afford 1,4-dicarbonyl compounds via cyclopropanation and subsequent ring opening.[20]



Scheme 3 Reactivity of enol ethers towards diazo reagents.

Our Cble-catalysed reaction allowed for functionalisation of not only these challenging substrates but also enamides **13** and vinyl sulfides **15** (Scheme 4). Although the list of substrates is not exhaustive is shows the potential of the reaction and some of its limitations.



Scheme 4 Scope of Cble-catalysed fuctionalisation of sp^2 CH bonds with EDA. [a]After treatment with TFA. [b]After hydrogenation.

In order to establish a mechanism, several experiments were conducted. Firstly, the formation of cyclopropane followed by ring opening was considered as an alternative pathway regardless of the fact that cyclopropane was not detected in our reaction but it could still act as a possible intermediate.[13,14] Hence, ethyl 2,2-diphenylcyclopropane-carboxylate[21] was subjected to the reaction conditions, but it was found to remain intact even after 24 h. On this basis the mechanism involving a cyclic intermediate was ruled out. Secondly, a series of Co(II) and Co(III) complexes were tested in the absence of a reducing agent (Table 4, entries 3, 4, 5) and in all cases compounds **4a**, **5a** were not observed contrary to reactions with the addition of a reductant (entry 6 and 7), lending support to our Co(I) theory. Thirdly, the ESI MS spectra of the crude reaction mixture (after 1 h) showed peaks at 1419.9 and 1718.9 suggesting species **17** and proving alkylcobalester **20** (see ESI; in MeOH, ligand exchange occurred) thus indicating the efficient formation of radical **A** and its fast addition to the double bond. In the absence of olefin **3a**, dimerization and reduction of diazoacetate occurred. The concentration of free radicals in the reaction mixture was too low to detect directly by EPR spectroscopy. Thus, the spin trapping experiment was performed by adding a spin trap (phenyl-*N*-*t*-butyl-nitrone) to the reaction mixture (see ESI).

Table 4 C-H-functionalisation of terminal olefins – mechanistic studies.[a]

Entry	Catalyst [mol%]	Light[b]	Reductant[c]	Yield [%][d]	4a : 5 ratio
1	Cble/1	LED	+	74	2.7 : 1
2	-	LED	-	-	-
3	$Co(acac)_2$/2	LED	-	-	-
4[e]	Cby/2	LED	-	-	-
5	Cble/2	LED	-	-	-
6	$Co(acac)_2$/2	LED	+	25	1 : 2.1
7	$CoCl(Ph_3P)_3$/2	LED	+	4	1 : 1
8	Co(TPP)	LED	+	23	15 : 1

[a]Conditions: 1,1-diphenylethene (0.5 mmol), EDA (1.5 mmol, 3 equiv.), catalyst, MeCN, light, 18 h. [b]LED – lamps. [c]Reductant: Zn, NH_4Cl. [d]Isolated yields. [e]Cby(II).[22]

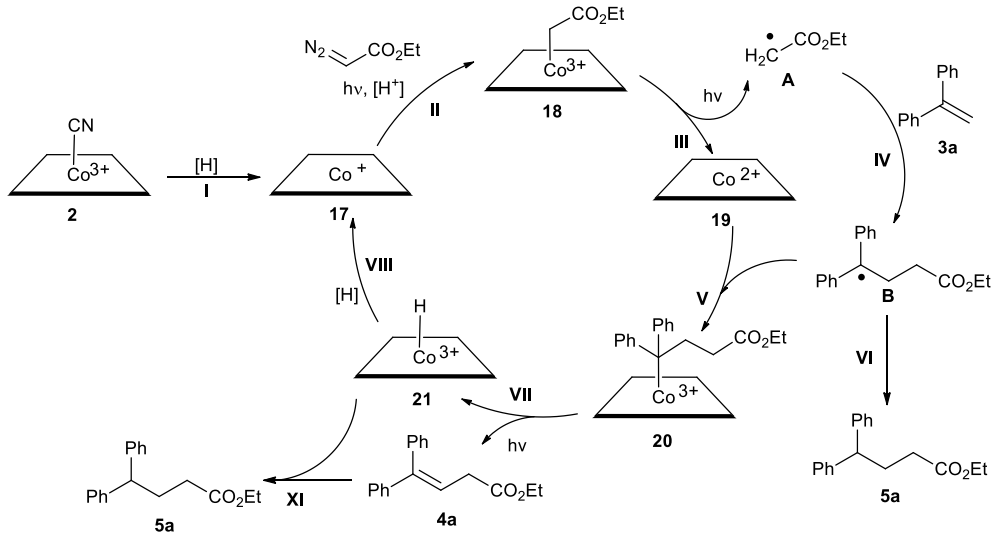
The formation of 'spin adducts' was ascertained supporting the radical mechanism. Moreover, addition of TEMPO, a radical scavenger, to the reaction mixture rendered it inactive.

The proposed mechanism for the cobalester-catalysed C-H insertion is shown in Scheme 5. Based on the experimental evidences, it is assumed to proceed via carbene transfer mechanism involving Co(I) species, contrary to previous reports. Firstly, cobalester (**2**) is reduced to the catalytically active Co(I) form **17** (**I**) which reacts with EDA affording alkyl cobalester(III) **18** (**II**) (see ESI). In this reaction, addition of proton present in complex **18** originates from NH_4Cl, which was clearly demonstrated by deuteration experiment (see ESI). Upon heating or light irradiation homolytic bond cleavage furnishes radical **A** (**III**). The subsequent, key C-C bond formation step involves the radical addition to the electron rich olefin (**IV**). Newly formed radical **B** can either recombine with Cble(II) species **19** possessing a radical character (**V**), abstract proton or disproportionate leading to by-product **5** (**VI**). Intermediate **20**, which presence was detected using ESI MS (see ESI) undergoes dehydrocobaltation generating desired product **4a** and hydridocobalester (Co(III)-H) **21** (**VII**) that upon reduction regenerates the catalyst (**VIII**) or reacts with olefin **4a** to produce unwanted by-product **5a** (**XI**).

Conclusions

In conclusion, we have demonstrated the use of vitamin B_{12} derivative **2** as a catalyst for the reaction of electron rich double bonds with EDA leading to unexpected insertion into olefinic sp^2 C-H bond instead of the usual cyclopropanation. The reaction is likely to proceed via a radical pathway involving the Co(I) species, allowing the formation of alkylcobalester intermediate, thus Cble **2** can be considered a 'reversible carrier' for an alkyl.

Our findings complement known reactivity of diazo compounds which now can be inserted not only into sp and sp^3 C-H bonds but also into sp^2 olefinic bonds. The developed methodology is not limited to electron-rich olefins but allows functionalisation of enol ethers, enamides, and vinyl sulfides. Moreover, this work gives solid foundation for future endeavors into diazo/vitamin B_{12} reactions, releasing its stronghold on cyclopropanation reactions. Further studies o



Scheme 5 Proposed mechanism.

on expanding this methodology are currently being undertaken and will be reported in due course.

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