C–C Coupling

International Edition: DOI: 10.1002/anie.201806799
German Edition: DOI: 10.1002/ange.201806799

Decarboxylative Negishi Coupling of Redox-Active Aliphatic Esters by Cobalt Catalysis

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Abstract: *A cobalt-catalyzed decarboxylative Negishi coupling reaction of redox-active aliphatic esters with organozinc reagents was developed. The method enabled efficient alkyl–aryl, alkyl–alkenyl, and alkyl–alkynyl coupling reactions under mild reaction conditions with no external ligand or additive needed. The success of an in situ activation protocol and the facile synthesis of the drug molecule (±)-preclamol highlight the synthetic potential of this method. Mechanistic studies indicated that a radical mechanism is involved.*

Transition-metal-catalyzed cross-coupling reactions to forge C–C bonds are of vital importance in modern organic synthesis.[1] While organohalides have enjoyed a success as the electrophilic coupling partners, recent years have witnessed a growing interest in the use of aliphatic carboxylic acids (or their derivatives) as alkyl halide surrogates in such reactions.[2] Advantages are apparent not only in the wide availability of carboxylic acids, but also in that alkyl halides are typically unstable, challenging to prepare, and undergo oxidative addition to transition metals with difficulty. By activating the carboxylic acid to the corresponding redox-active ester, single-electron-transfer reduction is feasible to generate an alkyl radical through the extrusion of CO_2. This radical-generation process has been involved in diverse carbon–carbon and carbon–heteroatom bond forming reactions based on single photocatalytic systems[3] or dual catalytic systems[4] combining photoredox catalysis with transition-metal catalysis.[5] Advances by the Baran research group showed that low-valent first-row transition metals, including nickel[6] and iron,[6h,g,7] were also effective in a broad range of decarboxylative cross-coupling reactions without the need for light irradiation. Very recently, a copper-catalyzed decarboxylative radical silylation of redox-active aliphatic esters was also developed.[8] Inspired by these elegant studies, we reasoned that a low-valent cobalt catalyst could also donate an electron to the redox-active ester,[9] thereby triggering alkyl radical formation and a follow-up cross-coupling reaction.

Cobalt, as an earth-abundant and low-toxic first-row transition metal, has been previously identified as an attractive catalyst enabling the effective coupling of aryl,[10] alkenyl,[11] and alkynyl halides[12] (or their pseudohalides) with organozinc compounds (Figure 1a). Nevertheless, the use of unactivated alkyl electrophiles[13] in cobalt-catalyzed Negishi coupling reactions is only recent.[14] In 2015, Knochel and co-workers reported an elegant cobalt-catalyzed cross-coupling reaction of (hetero)aryl zinc reagents with primary and secondary alkyl iodides; alkyl bromides were also applicable but with lower efficiency.[14a] We report herein a cobalt-catalyzed decarboxylative Negishi coupling of activated aliphatic carboxylic acids under mild reaction conditions (Figure 1b). The reaction allowed the synthesis of a broad range of alkylated arenes, alkenes, and alkynes by reactions with aryl zinc, alkenyl zinc, and alkynyl zinc reagents, respectively. In a decarboxylative alkynylation study reported by Baran and co-workers, $Co(acac)_2$ was shown to provide the desired product in 30% yield.[6j]

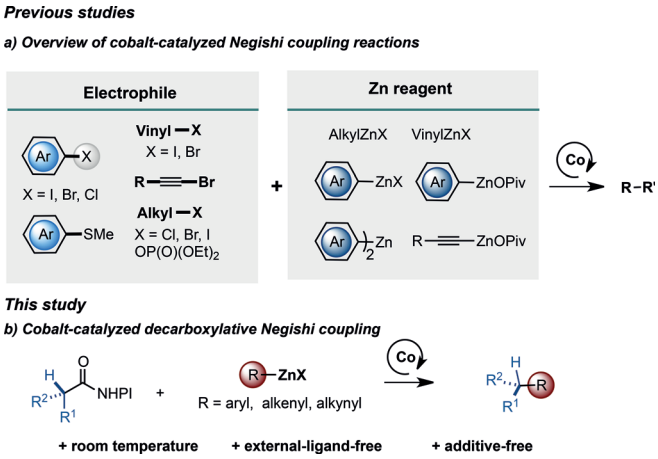

Figure 1. Cobalt-catalyzed Negishi cross-coupling reactions. Piv = pivaloyl.

We initiated our study by focusing on the coupling reaction of piperidine *N*-hydroxyphthalimide (NHPI) ester **1** with diaryl zinc reagent **2**. Systematic examination of different reaction parameters revealed that with $CoBr_2$ (10 mol%) as the catalyst in DMF at room temperature, the desired coupling product **3** could be formed in 75% yield [Eq. (1)].[15] The use of the tetrachloro-substituted NHPI ester TCNHP was also effective, but resulted in lower yield (44%). While the use of ultrapure $CoBr_2$ (99.99% purity) gave a similar yield, the omission of the catalyst led to no reaction, thus confirming that the cobalt salt is the active

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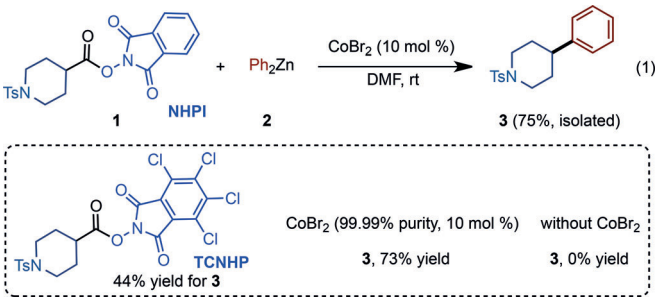
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201806799.



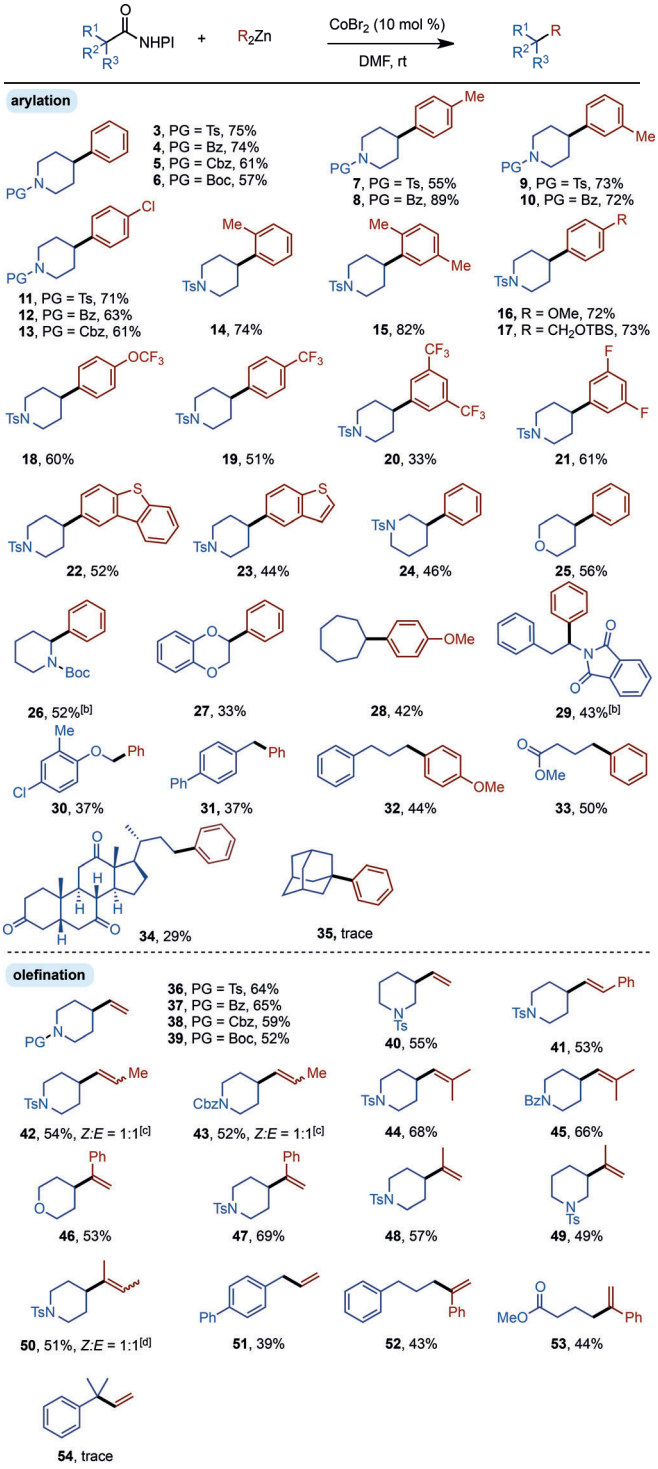
catalyst. A number of ligands were screened, but no improvement in the yield was observed.[15]

The scope of the reaction was explored extensively and found to be quite broad (Table 1). Diaryl zinc reagents bearing various functional groups were well tolerated, providing the expected decarboxylative arylation products **7**–**21** in good yields. Diheteroaryl zinc compounds were also applicable (products **22**, **23**). Besides *p*-toluenesulfonyl (Ts), other commonly encountered amino protecting groups, such as benzoyl (Bz; products **4**, **8**, **10**, **12**), carboxybenzyl (Cbz; products **5, 13**), and *tert*-butoxycarbonyl (Boc; products **6**, **26**) were compatible. Other heterocyclic (products **24**–**27**) and cyclic secondary carboxylic acids (product **28**), including those bearing an α-heteroatom (products **26**, **27**), were all viable substrates. Interestingly, N-protected phenylalanine could also be used to deliver the corresponding product **29**. Primary alkyl carboxylic acids yielded the desired products **30**–**34** as well. In general, the reactions of primary and secondary alkyl carboxylic acids showed comparable performance to the nickel[6a,h] and iron[6h,7] protocols developed by Baran and co-workers. However, in contrast to the protocol based on iron catalysis, a tertiary carboxylic acid substrate gave only a trace amount of product **35**, thus demonstrating a limitation of the current protocol. Product **18** is a valuable intermediate for the synthesis of Q203, a potent clinical candidate for the treatment of tuberculosis.[16]

The success of the decarboxylative arylation reaction promoted us to further examine the feasibility of a similar olefination reaction by treatment with alkenyl zinc reagents (Table 1).[6f] Under the above standard reaction conditions, the decarboxylative olefination reaction proceeded smoothly with exquisite control of olefin geometry to afford products **36**–**53**. Simple mono- (**36**–**40**, **51**), di- (**41**–**43**, **46**–**49**, **52**, **53**), and trisubstituted olefins (**44**, **45**, **50**) could be accessed readily, thus offering a simple and valuable retrosynthetic strategy for olefin synthesis. Once again, an attempt to couple a tertiary carboxylic acid substrate failed to give the desired product **54**.

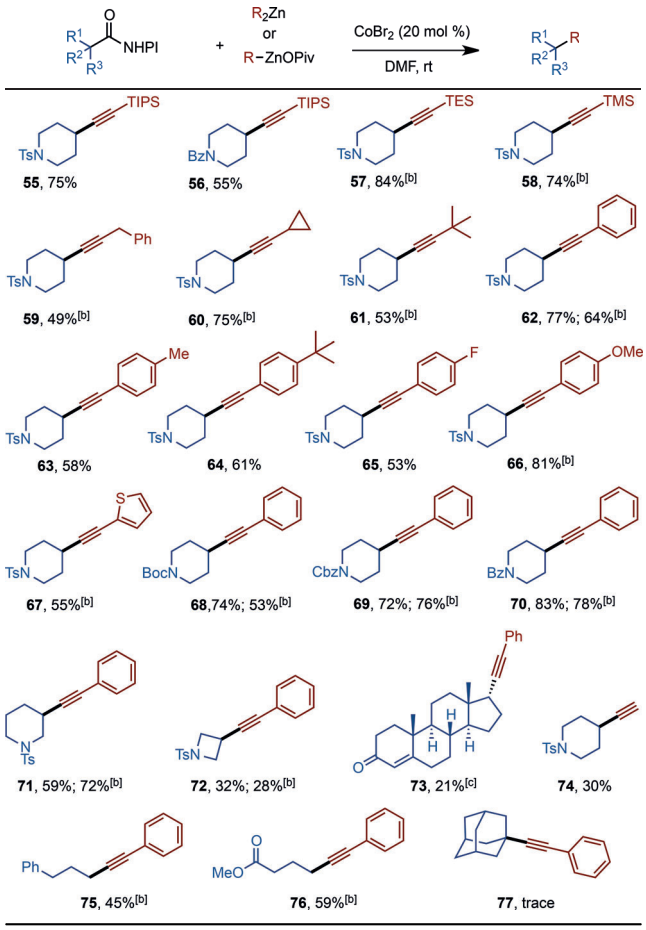
Alkynes are fundamentally important in functional molecules and organic synthesis. Methods for their synthesis through the transformation of aliphatic carboxylic acids should find broad application. We found that the use of dialkynyl zinc reagents as nucleophiles also led to efficient $C(sp^3)$–C(sp) bond formation (Table 2). Thus, a diverse arranges of silyl- (products **55**–**58**), aryl- (products **62**–**73**, **75**, **76**), and alkyl-substituted dialkynyl zinc reagents (products **59**–**61**) were well-suited for the coupling reaction, giving

Table 1: Scope of the cobalt-catalyzed decarboxylative alkyl–aryl and alkyl–alkenyl cross-coupling reactions.[a]



[a] Reaction conditions: redox-active ester (0.2 mmol), R_2Zn (0.66 mmol), $CoBr_2$ (10 mol%), in DMF (0.4 M), room temperature; yields are for the isolated product. [b] $CoBr_2$ (40 mol%). [c] The alkenyl zinc reagent was derived from a commercial Grignard reagent that exists as a mixture of olefin isomers. [d] The zinc reagent was prepared from the alkenyl bromide with a *Z*/*E* ratio of 1:1. Boc = *tert*-butoxycarbonyl, Bz = benzoyl, Cbz = carboxybenzyl, DMF = *N*,*N*-dimethylformamide, TBS = *tert*-butyldimethylsilyl, Ts = *p*-toluenesulfonyl.

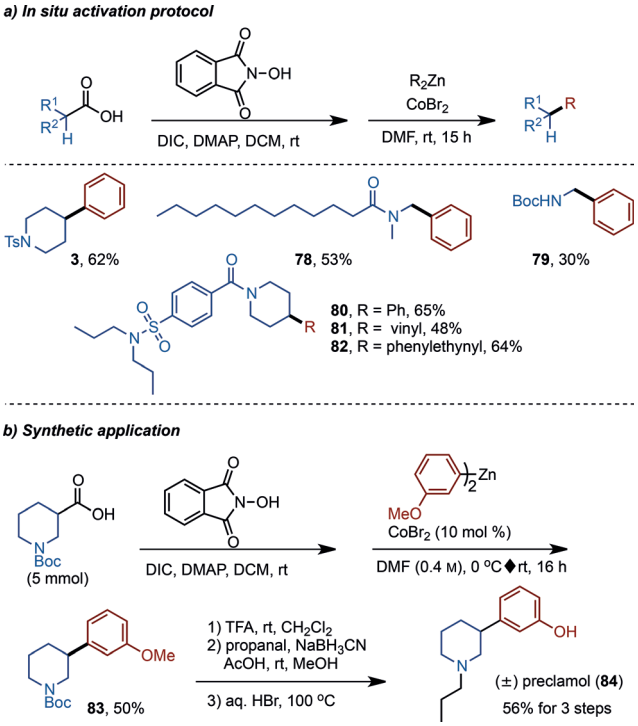
Table 2: Scope of the cobalt-catalyzed decarboxylative alkyl–alkynyl cross-coupling reaction.[a]



[a] Reaction conditions: redox-active ester (0.2 mmol), R_2Zn (0.66 mmol), $CoBr_2$ (20 mol%), in DMF (0.4 M), room temperature, 15 h; yields are for the isolated product. [b] RZnOPiv (3.0 equiv) was used. [c] RZnOPiv (4.0 equiv) was used. TES = triethylsilyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl.

the corresponding products in moderate to good yields. Diethynylzinc was also applicable as a reagent, but resulted in lower yield (product **74**). In some cases, the use of alkynyl zinc pivalates, recently introduced by Knochel and co-workers,[10d,g,14b,17] gave better yields. Baran and co-workers recently disclosed an elegant nickel-catalyzed decarboxylative coupling reaction of redox-active esters with alkynyl zinc chlorides.[6j] Although ethynylzinc worked efficiently in their method, other substituted alkynyl zinc reagents showed much less efficiency. Our cobalt protocol is therefore complementary to the method developed by Baran and co-workers.

An in situ activation protocol was developed to shorten the synthetic route. Thus, the free carboxylic acid was first coupled with *N*-hydroxyphthalimide in the presence of *N*,*N*′-diisopropylcarbodiimide (DIC) and DMAP in dichloromethane (DCM). After evaporation of the volatile components of the resulting mixture under vacuum, the residue was subjected to the cobalt-catalyzed Negishi-type decarboxylative cross-coupling reaction. The arylated product **3** was obtained in 62% yield, a yield slightly lower than that observed for the preactivation protocol [75%, Eq. (1)]. Primary carboxylic acids were also viable substrates for coupling (products **78**, **79**). Likewise, the olefination and alkynylation reactions could be carried out by following the same synthetic operations to give **81** and **82**, respectively (Scheme 1a).

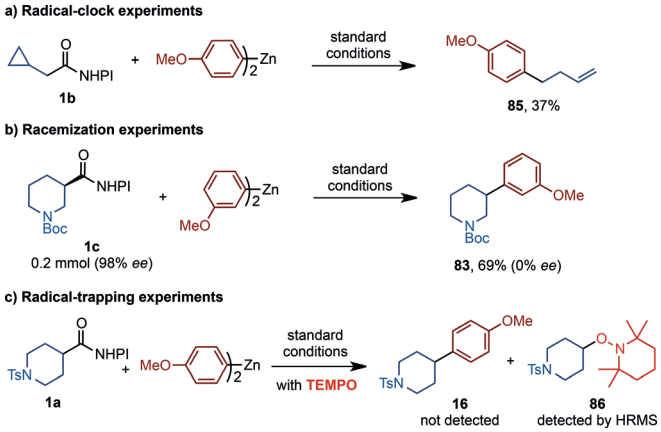


Scheme 1. In situ activation protocol and synthetic application. DMAP = 4-(dimethylamino)pyridine, TFA = trifluoroacetic acid.

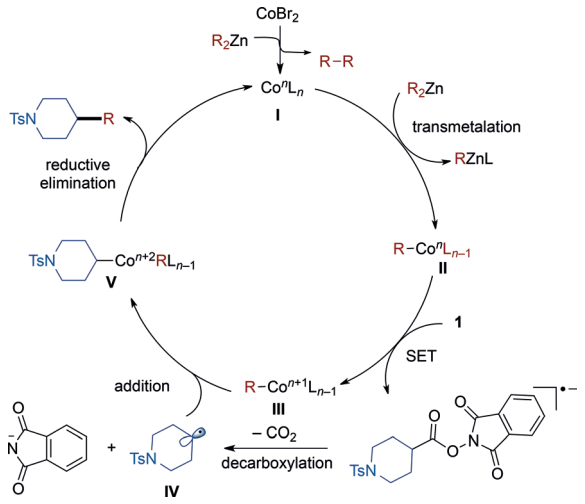
To showcase the utility of our method, we attempted the synthesis of the drug molecule (±)-preclamol. By using the in situ activation protocol, *N*-Boc-piperidine-3-carboxylic acid was first converted into the 3-arylated piperidine **83** in 50% yield. Thereafter, the removal of the *N*-Boc protecting group was followed by a reductive amination reaction by treatment with propanal in the presence of $NaBH_3CN$. Finally, the methoxy ether was hydrolyzed under acidic conditions to deliver the final product in 56% yield over three steps (Scheme 1b).

Mechanistic studies were conducted to shed light on the reaction mechanism. The involvement of radical intermediates in cobalt-catalyzed coupling reactions has been suggested previously.[10] To verify this possibility, we subjected the cyclopropyl-substituted substrate **1b** to the reaction, and a ring-opening arylation product **85** was produced (Scheme 2a). Furthermore, the reaction of **1c** with 98% optical purity led to complete racemization (Scheme 2b). Radical-trapping experiments with TEMPO shut down the reactivity, and a TEMPO adduct was detected by HRMS (Scheme 2c). All these results were in agreement with a radical reaction pathway.

On the basis of the above results and literature precedent,[6–9] we propose the reaction mechanism in Scheme 3.



Scheme 2. Mechanistic studies. TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl.



Scheme 3. Proposed mechanism.

Initially, the reduction of Co^{II} with the organozinc reagent forms the reactive low-valent cobalt catalyst **I**. This species then undergoes transmetalation with the organozinc reagent to generate intermediate **II**. Single-electron transfer (SET) from **II** to the NHPI ester triggers decarboxylative fragmentation to deliver a free radical **IV**, which then combines with the oxidized cobalt catalyst **III** to form a high-valent metal species **V**. Upon reductive elimination, the desired decarboxylative coupling product is produced and the reactive catalyst is regenerated.

In conclusion, we have developed an unprecedented cobalt-catalyzed decarboxylative cross-coupling reaction of activated aliphatic acids with organozinc reagents. The reaction proceeds under mild reaction conditions with no additive or external ligand necessary, leading to diverse arylation, olefination, and alkynylation products with good efficiency. The success of an in situ activation protocol further enhances the synthetic value of the reaction. Mechanistic studies pointed to the involvement of radicals in the reaction pathway.

Acknowledgements

Generous financial support from the Key Project of Chinese National Programs for Fundamental Research and Development (2016YFA0602900), the National Natural Science Foundation of China (21472250 and 21502242), the National Science and Technology Major Project of the Ministry of Science and Technology of China (2018ZX09735010), and the "1000-Youth Talents Plan" is gratefully acknowledged.

Conflict of interest

The authors declare no conflict of interest.

Keywords: C–C bond formation · cobalt · decarboxylation · Negishi coupling · redox-active esters

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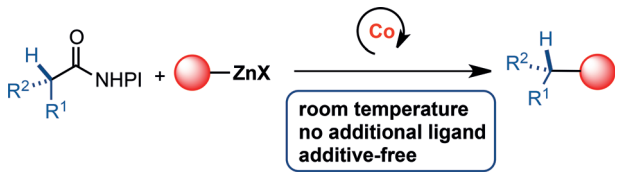
Manuscript received: June 12, 2018
Version of record online: ■■ ■■, ■■■■

Communications

C–C Coupling

X.-G. Liu, C.-J. Zhou, E. Lin, X.-L. Han, S.-S. Zhang, Q. Li, H. Wang* _____ ■■■■–■■■■

Decarboxylative Negishi Coupling of Redox-Active Aliphatic Esters by Cobalt Catalysis



Keen to couple: A cobalt-catalyzed decarboxylative Negishi coupling reaction of *N*-hydroxyphthalimide (NHPI) esters with organozinc reagents enabled efficient alkyl–aryl, alkyl–alkenyl, and alkyl–alkynyl coupling under mild conditions without an external ligand or additive (see scheme). The success of an in situ activation protocol and the facile synthesis of the drug molecule (±)-preclamol highlight the potential of this method.

