JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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Selective Intermolecular Oxidative Cross-Coupling of Enolates

Toru Amaya,*[,†] Yusuke Maegawa,[†] Takaya Masuda,[†] Yuma Osafune,[†] and Toshikazu Hirao*[,†,‡]

[†]Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Yamada-oka, Suita, Osaka 565-0871, Japan

[‡]ACT-C, Japan Science and Technology Agency (JST), 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan

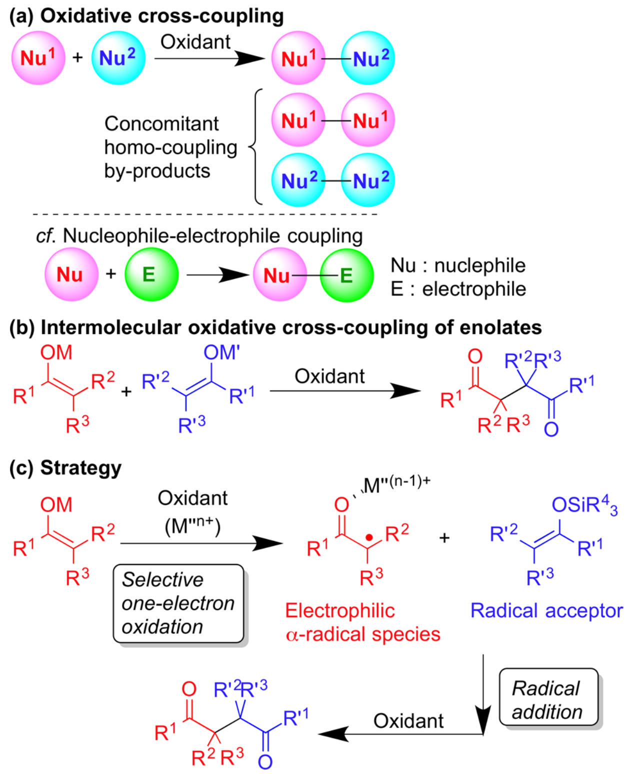
Supporting Information

ABSTRACT: Selective intermolecular oxidative cross-coupling of enolates, which is a bond-forming reaction between carbanion equivalents, remains as an unsolved issue despite its potential utility for the direct synthesis of unsymmetrical 1,4-diones. The main difficulty derives from the unavoidable homo-coupling. Our strategy depends on the selective one-electron oxidation of one enolate to afford an electrophilic carbonyl α-radical species, followed by trapping with another enolate. The present study demonstrates the selective oxovanadium(V)-induced cross-coupling between boron and silyl enolates.

Oxidative cross-coupling of carbon-centered nucleophiles leads to the formation of a new carbon−carbon bond, which is a complementary method to the conventional nucleophile−electrophile coupling (Scheme 1a). However, such cross-coupling of congeneric species is particularly challenging because of the lack of selectivity caused by the concomitant homo-coupling reaction.[1] More specifically, if the reaction is governed by only statistics, the ratio of homo-, cross-, and homo-coupling products is 1:2:1. Therefore, the development of versatile and selective intermolecular oxidative cross-coupling will definitely offer a useful strategy in retrosynthetic analysis of organic synthesis.

Our focus is on the intermolecular oxidative cross-coupling reaction of two different enolates (Scheme 1b). This reaction can provide a direct method to synthesize unsymmetrical 1,4-dicarbonyl compounds, which are found in naturally occurring products and medicinal compounds.[2,3] The first intermolecular oxidative cross-coupling was demonstrated between silyl enolates in 1975.[4] However, not much work has been done for over four decades, even including not only enolates also enamines as an enolate species.[5−19] The typical tactic relies on the stoichiometric advantage of one coupling partner (2−10-fold), whereas the yields generally remain about 50−80%.[4−12,14,17,18] We have also reported the oxo- and imidovanadium(V)-induced intermolecular cross-coupling of silyl enolates.[10,15] Reactivity differences also enable enolate species to undergo cross-coupling. For example, the higher reactivity (lower oxidation potential) of enamines compared with silyl enolates induces their cross-coupling.[9] Furthermore, enamine intermediates formed from aldehydes and a chiral amine catalyst oxidatively couple with silyl enolates asymmetrically.[14,18] The use of an α-stannyl carbonyl derivative in the presence of cerium(IV) oxidant also induces the cross-coupling reaction with silyl enolates.[11] The reactivity difference between imide enolates with a chiral auxiliary and ketone or ester

Scheme 1. (a) Oxidative Cross-Coupling; (b) Intermolecular Oxidative Cross-Coupling of Enolates; (c) Our Strategy for the Intermolecular Oxidative Cross-Coupling of Enolates



enolates as well as that between amides and ketone enolates provides practical yields (52−73%).[2,13] It should be emphasized that this research is one of the few examples[2,13,15,19] of equimolar cross-coupling to date. On the other hand, ketone enolate species are among the toughest combinations to cross-couple because of their similar reactivities,[4,6−12,16,17,19] where an auxiliary cannot be employed in contrast to the cases of esters, amides, and imides.[13] Selective cross-coupling of equimolar lithium enolates has been achieved by a strategy utilizing the selective heteroaggregation of lithium enolates by the steric effect, which is another one of the few examples of equimolar cross-coupling.[16] A sophisticated solution with an intramolecular traceless silicon tether of two different enolates has been developed.[3,20−22] However, the key bis(silyl) enolate

Received: May 21, 2015

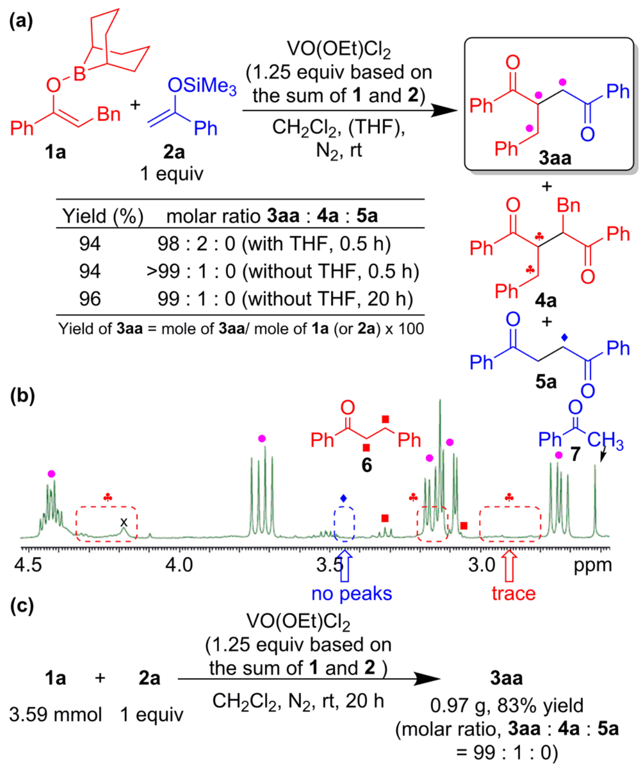
DOI: 10.1021/jacs.5b05058
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

requires several steps to prepare and the yields are moderate, which hampers convenience.

In this context, the present research was undertaken to develop the cross-coupling of ketone enolates with equimolar use of each coupling partner. Our working hypothesis depends on the distinction of roles for two enolates using different metals (M and M′). More specifically, this strategy includes two key steps: (1) selective one-electron oxidation of one enolate by a transition-metal oxidant M''^{n+} to give a Lewis acid-activated electrophilic carbonyl α-radical species[23] and (2) its radical addition with silyl enolate (M′ = SiR_3), which is known to behave as a radical acceptor[9,11,14] (Scheme 1c). On the other hand, we have studied the oxovanadium(V)-induced homo-coupling of boron enolates.[24] Our preliminary study suggested that boron enolate **1a** is more reactive than silyl enolate **2a** in the homo-coupling reaction and that the employed oxovanadium(V) oxidant leaves silyl enolate **2a** intact (Figure S1). Furthermore, stereoselective preparation of boron enolates has been established via trapping of the corresponding enolates[25] or hydroboration of α,β-unsaturated carbonyl compounds.[26] Therefore, boron enolates were chosen as the partner of silyl enolates. Here we report the intermolecular oxidative cross-coupling between equimolar boron and silyl enolates by $VO(OEt)Cl_2$ to give unsymmetrical 1,4-dicarbonyl compounds with high selectivity.

The investigation was initiated with the cross-coupling of boron enolate **1a** and silyl enolate **2a** using $VO(OEt)Cl_2$ (Scheme 2a), which is a Lewis acid with one-electron oxidation capability.[27] Boron enolate **1a** was prepared by hydroboration

Scheme 2. (a) Oxidative Cross-Coupling of Boron Enolate 1a and Silyl Enolate 2a; (b) Selected Region of the ^{1}H NMR Spectrum of the Crude Material after the above Cross-Coupling Reaction without THF for 20 h; (c) Gram-Scale Reaction



of chalcone with 9-borabicyclo[3.3.1]nonane (9-BBN) dimer or a tetrahydrofuran (THF) solution of 9-BBN to give the corresponding (Z)-enolate **1a** quantitatively. $VO(OEt)Cl_2$ (1.25 equiv based on the sum of **1a** and **2a**) was added to a CH_2Cl_2/THF solution of equimolar amounts of substrates **1a** and **2a** under nitrogen at room temperature, and then the reaction mixture was stirred for 30 min. To our surprise, this reaction afforded the desired cross-coupling product **3aa** selectively in 94% yield with a small amount of the homo-coupling product **4a** resulting from boron enolate **1a**, while the homo-coupling product **5a** resulting from silyl enolate **2a** was not observed in the ^{1}H NMR spectrum of the crude materials (molar ratio of cross-coupling product **3aa** and homo-coupling products **4a** and **5a** = 98:2:0). Furthermore, the same reaction without THF gave **3aa** with excellent selectivity in 94% yield. Small amounts of the compounds derived from protonation of both enolates **1a** and **2a** were observed as byproducts. Tracking the reactions with and without THF revealed that the reaction under the conditions with THF is much faster than that without THF but that the selectivity is a little lower (Figure S2). A longer reaction time (20 h) under the conditions without THF resulted in a yield of 96% with high selectivity. Scheme 2b shows the selected region of the ^{1}H NMR spectrum of the crude material. The obvious peaks for the homo-coupling product **5a** were not observed, but a small amount of the homo-coupling product **4a** and protonated species **6** and **7** were found. It should be noted that this reaction is applicable to almost gram-scale reaction without severe losses in yield and selectivity (83% isolated yield, **3aa**:**4a**:**5a** molar ratio = 99:1:0; Scheme 2c).

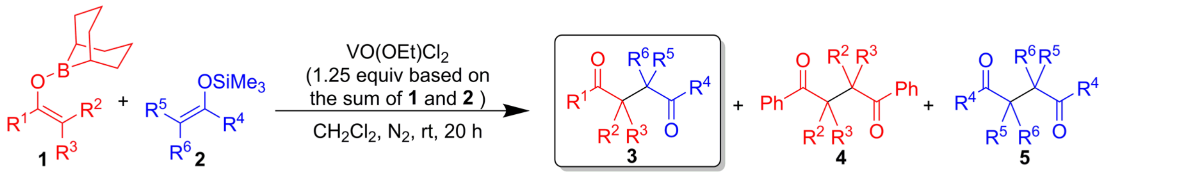
On the other hand, the use of lithium enolate **1a-Li** instead of boron enolate **1a** led to contrasting results (Figure S3): only a trace amount of cross-coupling product **3aa** was obtained, but homo-coupling product **4a** was formed in 31% yield. This selective homo-coupling of **1a-Li** in the presence of silyl enolate **2a** may be explained by aggregation of the lithium enolate,[16] which may facilitate its homo-coupling reaction.

This cross-coupling reaction depends on the oxidant (Table S1). The use of $VO(OPr\text{-}i)_2Cl$, which has lower oxidation capability and Lewis acidity,[28] gave rise to a low yield with low selectivity (51% yield, **3aa**:**4a**:**5a** molar ratio = 59:43:1). Other typical oxidants, including $[Ce(NO_2)_6](NH_4)_2$, $FeCl_3$, and $CuCl_2$, were not effective for the reaction, which may be partly due to their low solubility in CH_2Cl_2.

The scope of both boron and silyl enolates was explored with the above-optimized conditions (Table 1). Here the yields of cross-coupling products **3** are isolated yields (unless otherwise noted), and the selectivities are based on the molar ratios obtained from the ^{1}H NMR spectra of the crude materials. Cross-coupling of boron enolate **1a** and 4-fluorophenyl-substituted silyl enolate **2b** instead of **2a** took place in 99% yield with high selectivity (entry 1). Substituted boron enolate **1b** also selectively cross-coupled in 97% yield (entry 2). Boron enolates **1c**−**f** with a methyl group at the 2-position were employed for the oxidative cross-coupling with **2a** and **2b** to give good yields and selectivity (entries 3−10). The use of boron 1-cyclohexylprop-1-en-1-olate **1g** as an example of an aliphatic-substituted substrate afforded the cross-coupling products in good yields (77% for **3ga** and 84% for **3gb**) with high selectivity (entries 11 and 12). In the case of **2c** as an example of an aliphatic silyl enolate, the oxidative cross-coupling with boron enolate **1a** took place to give **3ac** in moderate yield and selectivity at −35 °C (entry 13). 1-Styryl-

DOI: 10.1021/jacs.5b05058
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 1. Oxidative Cross-Coupling of Boron Enolate 1 and Silyl Enolate 2[a]



Entry	Boron enolate 1	Silyl enolate 2	Cross-coupling product 3	Yield of 3 (%)[b]	Molar ratio[c] 3 : 4 : 5
1	1a	2b	3ab	99	99 : 1 : 0
2	1b	2a	3ba	97	99 : 1 : 0
3[d,e]	1c : R^7 = H	2a	3ca	97	96 : 4 : 0
4[e]	1d : R^7 = Me	2a	3da	97	93 : 7 : 0
5[f]	1e : R^7 = Cl	2a	3ea	88	93 : 7 : 0
6[f]	1f : R^7 = CF_3	2a	3fa	79	93 : 7 : 0
7[d,e]	1c	2b	3cb	98	95 : 5 : 0
8[e]	1d	2b	3db	97	92 : 8 : 0
9[f]	1e	2b	3eb	90	95 : 5 : 0
10[f]	1f	2b	3fb	72	93 : 7 : 0
11[f]	1g	2a	3ga	77	99 : 1 : 0
12[f]	1g	2b	3gb	84	99 : 1 : 0
13[g,h]	1a	2c	3ac	71[i]	83 : 17 : 0
14[j]	1h	2a	3ha	57	98 : 2 : 0
15	1i	2a	3ia	85	99 : 1 : 0
16[k]	1a	2d	3ad	91[i]	97 : 3 : 0
17[k]	1g	2d	3gd	63[i]	93 : 7 : 0
18	1f	2e	3fe	75 (*dr* = 71 : 29)	98 : 2 : 0[l]
19[g,h]	1a	2f	3af	85[i] (*dr* = 56 : 44)	94 : 6 : 0

[a]The **1**:**2** molar ratio was 1.0 unless otherwise mentioned. [b]Isolated yields. Yield of **3** = 100% × moles of **3**/moles of **1** (or **2**). [c]Determined by ^{1}H NMR analysis of the crude materials. [d]The reaction time was 17 h. [e]A small excess amount of **1** was employed (**1**:**2** ≈ 1.15:1). [f]The reaction time was 18 h. [g]A small excess amount of **2** was employed (**1**:**2** = 1:1.1). [h]The reaction temperature was −35 °C. [i]Determined by ^{1}H NMR analysis of the crude material based on an internal standard (1,3,5-trimethoxybenzene). [j]$VO(OEt)Cl_2$ (1.1 equiv relative to each enolate) was used. The reaction time was 0.5 h, and THF (33 equiv relative to **1h**) was added. [k]$VO(OPr\text{-}i)_2Cl$ (1.1 equiv relative to each enolate) was used. The reaction time and temperature were 24 h and −35 °C, respectively, and THF (33 equiv relative to **1**) was added. [l]The ratio was determined by isolation of **3fe** and **4f**.

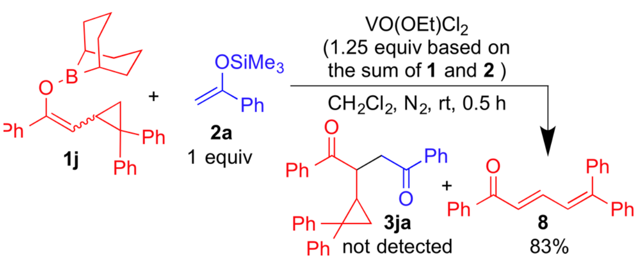
substituted boron enolate **1h** showed different reactivity, and the addition of THF was effective in this case to give the product **3ha** in moderate yield with high selectivity (entry 14). Introduction of two methyl groups at the 2-position of the boron enolate did not cause a problem in the yield and selectivity, and the corresponding cross-coupling product **3ia** having a quaternary carbon was obtained (entry 15). Up to here, selective cross-coupling was demonstrated in the combination of substituted boron enolates and unsubstituted silyl enolates at the 2-position. In the oxidative cross-coupling of ketone and ester enolates using $VO(OEt)Cl_2$, the homo-coupling product of the silyl enolate derived from the ester was

DOI: 10.1021/jacs.5b05058
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

observed because of the higher reactivity. Therefore, the conditions were reoptimized, and three key points were found: (1) the use of VO(OPr-*i*)$_2$Cl, (2) reaction with THF, and (3) low temperature (−35 °C). Consequently, the cross-coupling of boron enolate **1a** and silyl enolate **2d** gave the γ-keto ester **3ad** in 91% yield with high selectivity (**3ad**:**4a**:**5d** molar ratio = 97:3:0; entry 16). The use of an aliphatic boron enolate, **1g**, was not a problem for the cross-selectivity (entry 17). Finally, as an example of the most challenging combination, cross-coupling between ketone enolates monosubstituted at the 2-position (**1f** and **2e**) was carried out. Notably, the cross-coupling proceeded with high selectivity (75% yield, **3fe**:**4f**:**5e** molar ratio = 98:2:0; entry 18). Such selectivity is considered to be controlled by the difference in the reactivities of boron and silyl enolates. Oxidative cross-coupling of boron enolate **1a** and 1-(trimethylsiloxy)cyclopentene (**2f**) at −35 °C gave **3af** in 85% yield with **3af**:**4a**:**5f** molar ratio = 94:6:0 (entry 19).

To gain insight into the mechanism, a radical clock reaction was investigated using boron enolate **1j** with a cyclopropyl group at the 2-position (Scheme 3). Boron enolate **1j** was

Scheme 3. Radical Clock Reaction



treated with VO(OEt)Cl$_2$ in the presence of silyl enolate **2a** and afforded the ring-opened product **8** in 83% yield; the cross-coupling product **3ja** was not detected. This result suggests the formation of carbonyl α-radical species. The detailed mechanism needs more investigation (we try to show a plausible reaction path in Figure S4), but the expected strategy shown in Scheme 1c is considered to operate in this cross-coupling.

In conclusion, the oxovanadium(V)-induced oxidative cross-coupling between boron and silyl enolates was achieved in high yields with high selectivity. One of the keys for this reaction system is the choice of the combination of boron and silyl groups as metals for the enolates, providing a reactivity difference. Scale-up to almost a gram scale was performed. The substrate scope revealed that substituted boron enolates from ketones and silyl enolates can be employed for selective cross-coupling. The developed selective intermolecular oxidative cross-coupling of enolates will bring significant benefit for the straightforward synthesis of unsymmetrical 1,4-dicarbonyl compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05058.

Figures S1−S5, Table S1, synthetic procedures, characterization data, and NMR charts of the products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*amaya@chem.eng.osaka-u.ac.jp

*hirao@chem.eng.osaka-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from JST (ACT-C) is acknowledged. This work was also partially supported by a Grant-in-Aid for Scientific Research (C) (26410046) from the Japan Society for the Promotion of Science.

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DOI: 10.1021/jacs.5b05058
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX