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Cobalt/Rhodium-Catalyzed Diversified Amidation of Benzocyclobutenols via C−C Cleavage under Catalyst and Condition Control

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Cite This: https://doi.org/10.1021/acs.orglett.3c01788 Read Online

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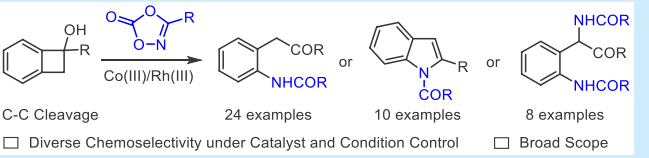
ABSTRACT: Cobalt(III) and rhodium(III)-catalyzed regio- and chemoselective amidation of benzocyclobutenols has been realized using dioxazolone as the amidating reagent to afford three classes of C−N-coupled products via β-carbon elimination of the benzocyclobutenol. The Co(III)-catalyzed coupling initially afforded an isolable *o*-(*N*-acylamino)arylmethyl ketone, which could further cyclize to the corresponding indole derivatives under condition control. In contrast, efficient stepwise diamidation has been achieved under Rh(III) catalyst control. The chemoselectivities are jointly controlled by the catalyst and reactions conditions.



In the past decades, increasing attention has been devoted to the selective cleavage and functionalization of C−C bonds because of the abundance of C−C bonds in almost every organic compound.[1] Given the low reactivity and steric hindrance of common C−C bonds, the substrate activation strategy is typically adopted, as in metal-catalyzed C−C activation of strained three/four-membered-rings, which provides a feasible and powerful avenue toward rapid assembly of complicated new scaffolds because of facile scaffold reconstruction.[2] Along this line, great efforts have been devoted to the functionalization of benzocyclobutanone[3] and derivatives.[4] Dong and co-workers used the "cut-and-sew" strategy, which involved metal-catalyzed C−C bond functionalization by oxidative addition and coupling with unsaturated reagents.[5] As a direct derivative of benzocyclobutanone, benzocyclobutenol also reacted in high activity and regioselectivity in intermolecular reactions via selective cleavage of the $C(sp^2)-C(sp^3)$ bond.[6−14] To date, metal-catalyzed C−C activation of benzocyclobutanols has been carried out in three reaction modes (Scheme 1). First, the Orellana group reported Pd-catalyzed regioselective $C(sp^2)-C(sp^2)$ coupling of benzocyclobutenols with aryl bromides (Scheme 1a-1).[7] Second, Murakami et al. pioneered the Rh(I)-catalyzed C−C activation of benzocyclobutenols en route to intermolecular [4 + 2] annulation with various π-bonds, which affords six-membered ring alcohol (Scheme 1a-2).[8] Since then, extensive studies on C1−C2 cleavage of benzocyclobutenols has been realized by Rh(I) catalysis, and annulation reactions with alkene,[9] alkyne,[10] allene,[11] and isocyanate[12] have been disclosed. This type of coupling has also been extended to intramolecular systems by taking advantage of the resulting ketone moiety. For example, Shi and Song et al. recently realized Rh(I)-catalyzed cyclization of alkene-tethered benzocyclobutenols followed by hydrogentransfer, which results in the formation of benzofurans bearing a 4-β-hydroxy or 4-β-keto moiety (Scheme 1a-3).[13] In the third category, Wang reported in 2014 a Rh(I)-catalyzed [4 + 1] ring expansion reaction of benzocyclobutenol, which utilizes diazoesters as a C_1 precursors to afford indanols with an all-carbon quaternary center (Scheme 1a-4).[14]

Most reported results in the C−C activation of benzocyclobutenols have focused on $C(sp^2)-C(sp^3)$ or $C(sp^2)-C(sp^2)$ bond formation. In this regard, the applications of benzocyclobutenols toward construction of *C*-heteroatom bonds would be of great interest. Given the nucleophilic nature of the benzocyclobutenol reagent, we hypothesized the employment of a heteroatom electrophilic reagent that matches the reactivity of the M−C(aryl) bond resulting from β-carbon elimination of a benzocyclobutenol. In that context, 1,4,2-dioxazol-5-one proved highly reactive as a nitrene transfer reagent under Co,[15] Rh,[15b,16] and Ir.[15b,17] In addition, the initial coupling generates a nucleophilic NH group tethered to an electrophilic carbonyl, which may readily undergo cyclization−condensation. We now report the efficient synthesis of three classes of C−N-coupled products in excellent regio- and chemoselectivity that are under catalyst and condition control (Scheme 1b).

Initially, the reaction of benzocyclobutenol (**1a**) with 1,4,2-dioxazol-5-one (**2a**) was screened to identify the optimal reaction conditions (Table 1). An optimal isolated yield of 91% of product **3aa** was obtained when catalyzed by

Received: June 1, 2023

Scheme 1. C−C Bond Cleavage of Benzocyclobutenols

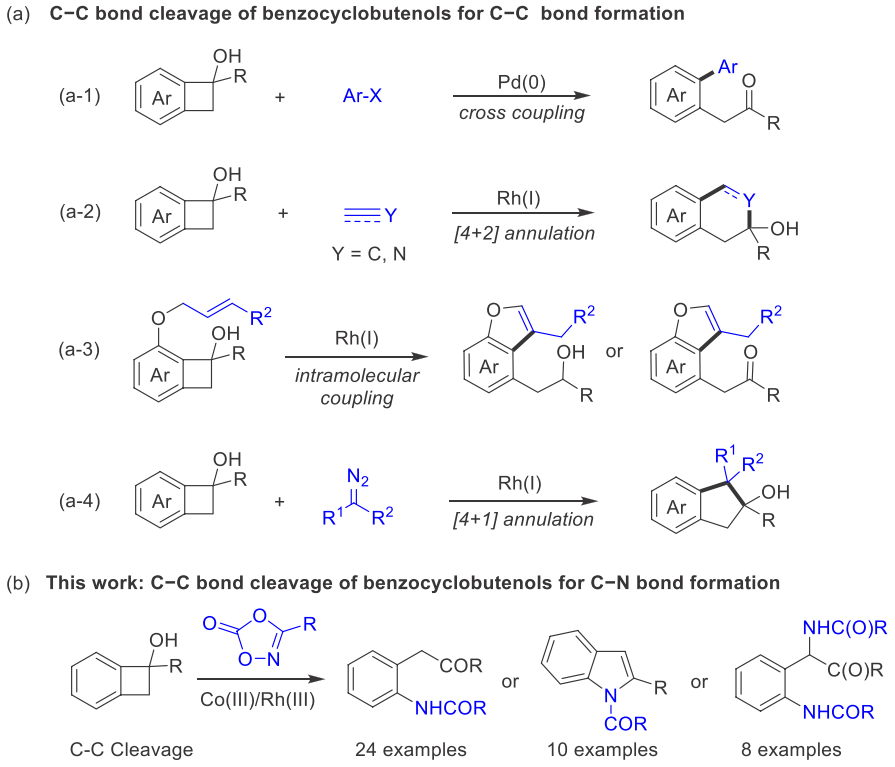
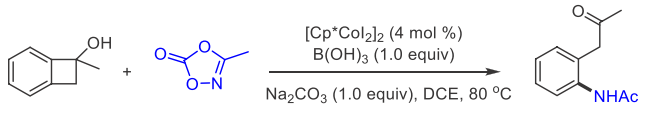


Table 1. Optimization Studies of the Amidation Reaction[a-c]



entry	variations from conditions	yield (%)
1	none	91 (91)
2	$[Cp^*Co(CO)I_2]$ instead of $[Cp^*CoI_2]_2$	80
3	$[Cp^*IrCl_2]_2$ instead of $[Cp^*CoI_2]_2$	N.D.
4	$[(p\text{-cymene})RuCl_2]_2$ instead of $[Cp^*CoI_2]_2$	N.D.
5	without $[Cp^*CoI_2]_2$	N.D.
6	without additive	30
7	without Na_2CO_3	84
8	Ag_3PO_4 (0.2) as additive	69
9	Ag_2CO_3 (0.2) as additive	45
10	AgOAc (0.2) as additive	33
11	without $B(OH)_3$	37
12	MeCN as solvent	12
13	THF as solvent	38
14	DCM as solvent	74

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $[Cp^*CoI_2]_2$ (4 mol %), and an additive in a solvent (1.0 mL) at 80 °C for 1 h under N_2. [b]The yield was determined by crude ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard; isolated yield is indicated in parentheses. [c]N.D. = not detected.

$[Cp^*CoI_2]_2$ (4 mol %) in the presence of $B(OH)_3$ and Na_2CO_3 as the additives in 1,2-dichloroethane (DCE) at 80 °C for 1 h (entry 1). In contrast, other catalysts, such as $[Cp^*Co(CO)I_2]_2$, $[Cp^*IrCl_2]_2$, and $[(p\text{-cymene})RuCl_2]_2$, were all less active or completely inactive (entries 2−4). No desired product was detected when $[Cp^*CoI_2]_2$ was omitted (entry 5). Further investigation of additives revealed that Lewis acid seemed to provide the desired product in good yield, and $B(OH)_3$ performed best to give 84% yield (entries 6−10). $B(OH)_3$ may play a pivotal role in activating dioxazolone toward migratory insertion of the nitrene and suppressing the background reaction of a base-mediated simple ring opening. The yield was further increased by the addition of Na_2CO_3, which increased yield slightly when added alone (entry 11). Solvent screening revealed that DCE was superior to others (entries 12−14).

With the optimized reaction conditions in hand, the scope and generality of this coupling system was examined (Scheme 2). A range of dioxazolones **2** with diverse steric and electronic properties, such as Me, Et, ^{i}Pr, ^{n}Bu, and cyclopropyl, reacted in high reactivity under the standard reaction conditions (**3aa**−**3ae**). In comparison, dioxazolones bearing an aryl group (Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, and 4-$NO_2C_6H_4$) generally exhibited lower reactivity, and a prolonged reaction time was necessary to ensure moderate reactivity (**3af**−**3al**). In addition, 3-(2-furanyl)-1,4,2-dioxazol-5-one also reacted to give the target product (**3ag**, 46% yield).

Next, the scope of benzocyclobutenols was investigated in the reaction with 3-methyl-1,4,2-dioxazol-5-one (Scheme 2). Benzocyclobutenols bearing diverse alkyl or aryl groups, such as Et, ^{i}Pr, Cy, Bn, cyclopropyl, and Ph, were all tolerated regardless of the electronic effect, thereby affording the corresponding products **3ba**−**3ga** in good yield. Variation of the aromatic ring in the benzocyclobutenols was also successful, as in the smooth reaction of 5-Me-, 4-Me-, 4-OMe-, 4,5-dimethoxy-, and 3-Cl-substituted benzocyclobutenols (**3ha**−**3la**). Extension to a 2-naphthalene-based substrate was also successful (**3ma**, 61% yield).

During our optimization studies, an annulated indole such as **4aa** was detected when the reaction was conducted for a

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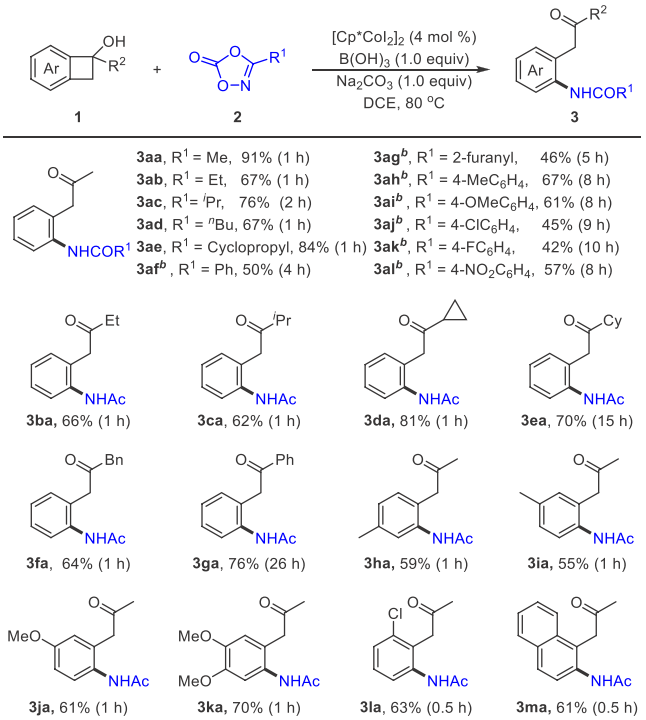
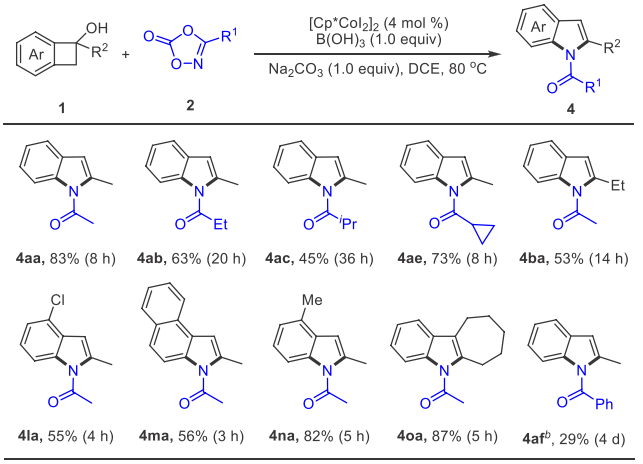
Scheme 2. Substrate Scope of the Amidation of Benzocyclobutenols with Dioxazolones[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[Cp^*CoI_2]_2$ (4 mol %), $B(OH)_3$ (1.0 equiv), and Na_2CO_3 (1.0 equiv) in DCE at 80 °C under N_2; isolated yield. [b]Compound **1** (0.1 mmol), **2** (0.15 mmol), $[Cp^*CoI_2]_2$ (4 mol %), and Na_3PO_4 (0.2 mmol) at 60 °C in DCM under N_2; isolated yield.

prolonged reaction time, which suggested that the *o*-(*N*-acylamino)arylmethyl ketones **3** might undergo further cyclization via condensation. The scope of this indole synthesis was then explored (Scheme 3). This transformation was successfully extended to several other dioxazolones and benzocyclobutenols. Dioxazolones with different 3-alkyl groups

Scheme 3. Substrate Scope of Co-Catalyzed Annulation between Benzocyclobutenols and Dioxazolones[a,b]

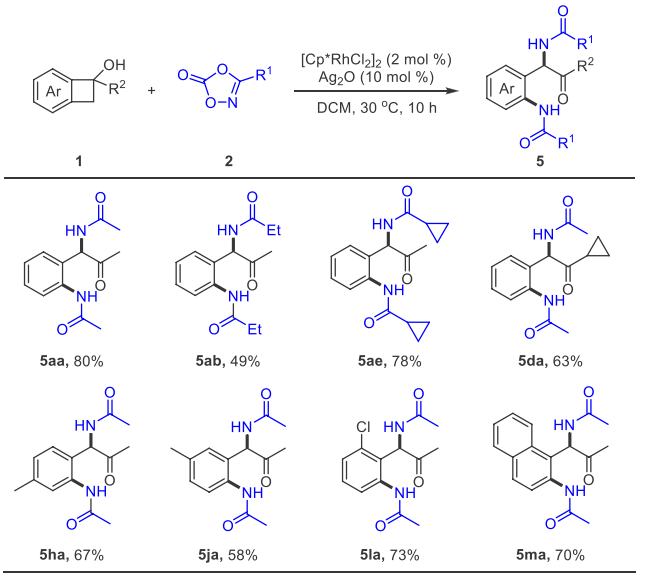


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[Cp^*CoI_2]_2$ (4 mol %), $B(OH)_3$ (1.0 equiv), and Na_2CO_3 (1.0 equiv) in DCE at 80 °C under N_2; isolated yield. [b]At 130 °C.

all reacted well (**4aa**−**4ae**, 8−36 h). Benzocyclobutenol bearing a 1-ethyl group afforded the corresponding indole derivative in 43% yield (**4ba**). Benzocyclobutenols with 6-Cl, 6-Me, and a fused ring all quickly delivered the desired products in satisfactory yield (**4la**−**4na**, 3−5 h). We postulated that this facile condensation was facilitated by the steric effect of these substituents (steric assistance). Significantly, a ring-fused benzocyclobutenol also reacted to deliver the desired product in excellent yield (**4oa**). A phenyl-substituted dioxazolone could also afford the corresponding product **4af**, albeit under harsh conditions.

Because of the powerful role of rhodium catalyst in amidation reactions,[16,18] an efficient diamidation reaction was realized when catalyzed by $[Cp^*RhCl_2]_2$ under rather mild reaction conditions with Ag_2O (0.1 equiv) as an additive (see Scheme 4 and Table S1). With dioxazolone as the limiting

Scheme 4. Substrate Scope of Diamidation of Benzocyclobutenols with Dioxazolones[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2 mol %), and Ag_2O (10 mol %) in DCM at 30 °C under N_2; isolated yield.

reagent, diamidation product **5aa** was isolated in 80% yield. The formation of this product is interesting because it involved sequential cleavage of a C−C bond and a $C(sp^3)$−H bond. Variation of the dioxazolones to different 3-alkyl groups (Me, Et, and cyclopropyl) was successful, which afforded the products **5aa**, **5ab**, and **5ae**. The presence of alkyl, halo, and fused rings was also well-tolerated (**5ha**, **5ja**, **5la**, and **5ma**) (Scheme 4).

We next performed a series of experimental investigations to explore possible reaction mechanisms (Scheme 5). Control experiments using propiophenone as a substrate failed to give any amidating product under the standard Co-catalyzed conditions. These results indicated that the key cobalt aryl species was formed via C−C bond cleavage rather than C−H bond activation, and no reversible *ortho*-C−H activation should be involved. The role of the catalyst and/or the additive during the cyclization−condensation process was next examined. Heating a solution of **3aa** in the presence of $[Cp^*CoI_2]_2$ or both $[Cp^*CoI_2]_2$ and $B(OH)_3$ gave product

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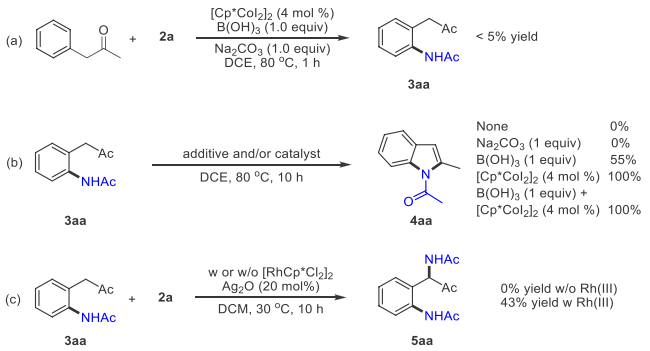
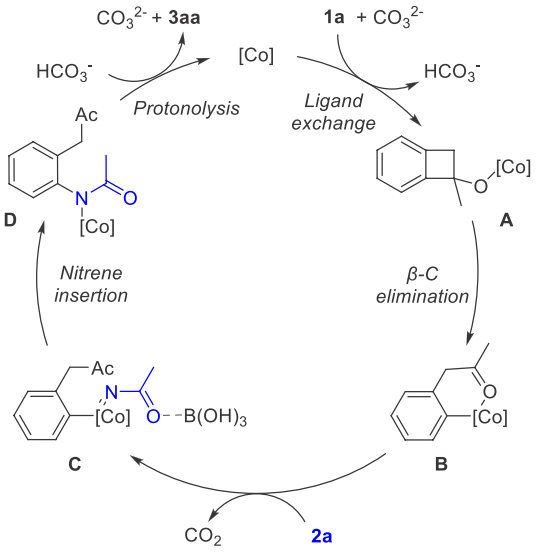
Scheme 5. Mechanistic Studies



Scheme 6. Proposed Catalytic Cycle



3aa in 100% yield, while the employment of $B(OH)_3$ alone only gave cyclization product **4aa** in 55% yield (Scheme 5b). No conversion was observed when Na_2CO_3 alone was used. These observations highlighted the primary Lewis acidic nature of the Co catalyst in the cyclization of *o*-(*N*-acylamino)-arylmethyl ketones. To further explore the process of the cyclization, we graphed the yield−time distribution curves of **3ae** and **4ae** by ^1H NMR analysis (Supporting Information). Initially, **3ae** was generated in a short time. As the reaction proceeded, it subsequently decayed with the increase in the amount of **4ae**, thereby indicating the intermediacy of **3ae**.

To further explore the mechanistic details of the diamidation system, an equimolar mixture of **3aa** and **2a** was allowed to react under the standard conditions, from which complex **5aa** was isolated in 43% yield. This result indicated a sequential diamidation approach (Scheme 5c). In contrast, no diamidation product was detected in the absence of $[Cp^*RhCl_2]_2$, which suggested the important role of Rh(III) in the second amidation. A crossover experiment using benzocyclobutenol **1a** and two distinguishable dioxazolones verified that the diamidation reaction is stepwise because two corresponding crossover products (**8** and **9**) were generated (see Figure S1, Supporting Information).

Synthetic applications have been performed (see the Supporting Information for details). Scale-up reaction of **1a** and **2a** afforded the corresponding product **3aa** in 73% yield. Transformations of indole **4aa** were also conducted to showcase its synthetic utility. The C−H alkenylation reaction of **4aa** with an alkynyl bromide afforded **6** in 97% yield, and the oxidation reaction of **4aa** provided nitrile **7** in 58% yield.

A catalytic cycle is proposed in Scheme 6 on the basis of the above reaction results and related reports.[13] An alkoxide intermediate **A** is generated via ligand exchange between Cp*Co(III) and **1a** in the presence of a base, which is then proposed to undergo regioselective *β*-C elimination to give a Co−C(sp^2) species **B**. Coordination of **2a** and subsequent decarboxylation deliver a nitrene intermediate **C**, possibly with the assistance of $B(OH)_3$. Migratory insertion of the Co−C bond into the nitrene unit is proposed to give intermediate **D**, again with possible assistance of the $B(OH)_3$ additive. Protonolysis of intermediate **D** furnishes the final product and regenerates the catalyst.

In conclusion, we disclosed diversified amidation reactions between benzoclobutenol and dioxazolone via Co(III)- or Rh(III)-catalyzed C−C bond cleavage. Three classes of C−N-coupled products have been selectively obtained in moderate to excellent efficiency via *β*-carbon elimination of the benzocyclobutenol. The Co(III)-catalyzed coupling initially afforded an isolable *o*-(*N*-acylamino)arylmethyl ketone, which could further cyclize to the corresponding indole derivatives under condition control. In contrast, efficient stepwise diamidation has been attained under Rh(III) catalyst control. Overall, the chemoselectivities are jointly controlled by the catalyst and reaction conditions. The generation of reactive metal−carbon species using other common substrates is underway in our laboratories, which may offer new possibilities for the synthesis of complex scaffolds.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01788.

Detailed experimental procedures, characterization of new compounds, and copies of NMR spectra (PDF)

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https://doi.org/10.1021/acs.orglett.3c01788
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the NSFC (22101167) and the SNNU is gratefully acknowledged.

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https://doi.org/10.1021/acs.orglett.3c01788
Org. Lett. XXXX, XXX, XXX−XXX