Catalytic Dealkylative Synthesis of Cyclic Carbamates and Ureas via Hydrogen Atom Transfer and Radical-Polar Crossover

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ABSTRACT: Guided by the transition metal hydrogen atom transfer and radical-polar crossover concept, we developed a catalytic, Markovnikov-selective, functional-group tolerant, and scalable synthesis of cyclic carbamates, which are found in the structures of many bioactive compounds. This method not only provides common oxazolidinones but also six-to-eight-membered ring products. The reaction proceeds through the intramolecular displacement of an alkylcobalt(IV) intermediate and dealkylation by 2,4,6-collidine; the activation energies of these steps were calculated by DFT. Cyclic ureas and cyclic phosphoramidates were also synthesized under the same reaction conditions.

Much effort has been devoted in modern synthetic organic chemistry to the development of diverse methods for hydrofunctionalizing alkenes through transition-metal hydrogen-atom-transfer (TM-HAT) processes.[1] A transition metal hydride generated *in situ* from a catalyst and a hydrogen source reacts with the alkene unit to chemoselectively generate a carbon-centered radical that then becomes involved in diverse transformations (**Scheme 1A**).[2] Recently, this mechanism has been shown to operate in conjunction with other transition metal catalysis mechanisms, thereby expanding the scope of the transformation.[3]

Our group has independently shown that the addition of an *N*-fluorocollidinium salt to a commonly used cobalt-Schiff base catalyst and a silane facilitates radical-polar crossover (RPC) to generating a cationic alkylcobalt(IV) intermediate. To date, we have disclosed that oxygen-,[4] nitrogen-,[5] carbon-,[6] and sulfur[7] nucleophiles react with these cationic species in TM-HAT chemistry. Among them, the formation of a lactone from an alkenyl ester is a profound example for us (**Scheme 1B**).[4a] In the light of related reports,[2q,2r,7-8] it is plausible that the sp²-oxygen atom of the carbonyl group attacks the reactive cationic carbon of the alkylcobalt(IV) intermediate to release a cobalt(II) complex, after which removal of the methyl group by 2,4,6-collidine led to the lactone. Indeed, we computed the activation energies for the steps involving **TS-a** and **TS-b** to be only 11.0 and 14.1 kcal/mol, which suggests that these two steps are possible. With the aim of expanding the substrate scope, the promising reactivity of the TM-HAT/RPC mechanism prompted us to design further cyclization reactions that involve poorly nucleophilic species.

Herein, we report the dealkylative cyclizations of alkenyl carbamates and alkenyl isoureas to afford cyclic carbamates and cyclic ureas, respectively (**Scheme 1C**). Cyclic carbamates and ureas are important structural motifs found in pharmaceuticals and bioactive agents, such as linezolid (antibiotic active against VRE and MRSA),[9] efavirenz (anti-HIV drug),[10] biotin (cofactor),[11] and aquiledine (natural product).[12] This observation encouraged synthetic chemists to develop various preparative methods for cyclic carbamates[13] and cyclic ureas.[14] However, to the best of our knowledge, the substrate scope of most reactions is limited to only common five- and six-membered rings, and examples of medium ring formation are rather rare.[13a,14g] On the other hand, the method described here provides five- to eight-membered ring compounds.
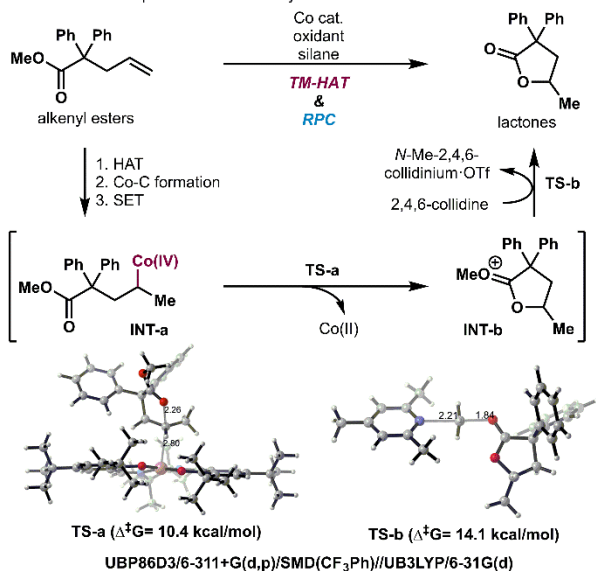
We commenced by determining an appropriate carbamate structure using previously developed reaction conditions: cobalt catalyst **C1**, *N*-fluoro-2,4,6-collidinium trifluoromethanesulfonate (**3**), and 1,1,3,3-tetramethyldisiloxane in benzotrifluoride at room temperature (**Scheme 2**). Although the desired oxazolidinone **2** was obtained from all substrates **1a–1c**, we found that *tert*-butyl carbamate **1c** gave the best results. It should be noted that the methyl ester gave a better yield than the corresponding *tert*-butyl ester in the previously reported dealkylative cyclization that affords lactones.[4a] We also observed coproducts **4** in 196% yield from **1c**. Therefore, the deprotonation of the *tert*-butyl group by 2,4,6-collidine occurs after cyclization of the alkylcobalt(IV) intermediate. The activation energies for the steps involving **TS-c** and **TS-d** were calculated to be only 12.6 and 7.2 kcal/mol (without the OMe group to reduce calculational costs),
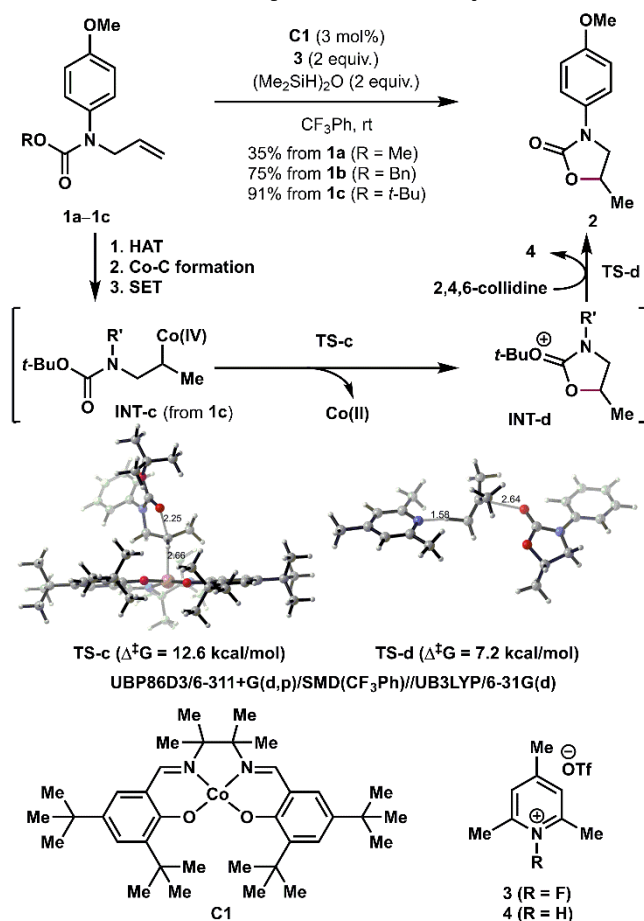
Scheme 1. TM-HAT and RPC mechanism

(A) TM-HAT catalyzed reaction

(B) Cyclization of esters to afford lactones via TM-HAT/RPC and DFT calculations for transition states of displacement and dealkylation[a]
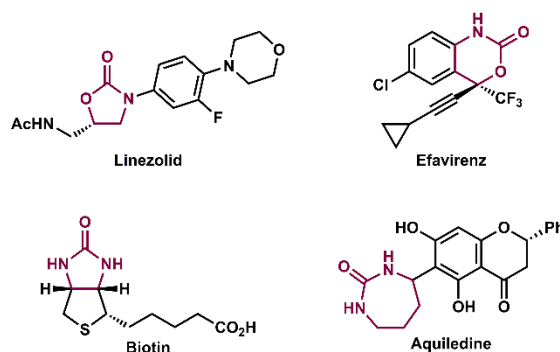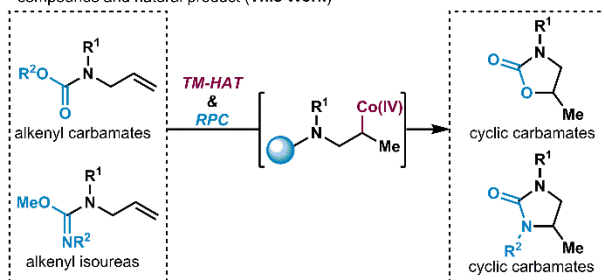

TS-a ($\Delta^{\ddagger}$G= 10.4 kcal/mol)   TS-b ($\Delta^{\ddagger}$G= 14.1 kcal/mol)

UBP86D3/6-311+G(d,p)/SMD(CF$_3$Ph)//UB3LYP/6-31G(d)

(C) Cyclization to afford cyclic carbamates & ureas via TM-HAT/RPC and biologically active compounds and natural product (**This Work**)

alkenyl carbamates → cyclic carbamates

alkenyl isoureas → cyclic carbamates

Linezolid

Efavirenz

Biotin

Aquiledine

Scheme 2. Initial attempt of oxazolidine synthesis[a]

35% from **1a** (R = Me)
75% from **1b** (R = Bn)
91% from **1c** (R = t-Bu)

TS-c ($\Delta^{\ddagger}$G = 12.6 kcal/mol)   TS-d ($\Delta^{\ddagger}$G = 7.2 kcal/mol)

UBP86D3/6-311+G(d,p)/SMD(CF$_3$Ph)//UB3LYP/6-31G(d)

C1

3 (R = F)
4 (R = H)

The reactions of **1a–1c** (0.20 mmol) were performed in the presence of **C1** (3 mol%), **3** (2.0 equiv.), 1,1,3,3-tetramethyldisiloxane (2.0 equiv.) in benzotrifluoride (2.0 mL) at room temperature for 18 h under argon. Isolated yields are shown. DFT calculations were performed for the synthesis of **5** to reduce calculational costs.

which suggests that the mechanism shown in **Scheme 2** is feasible.
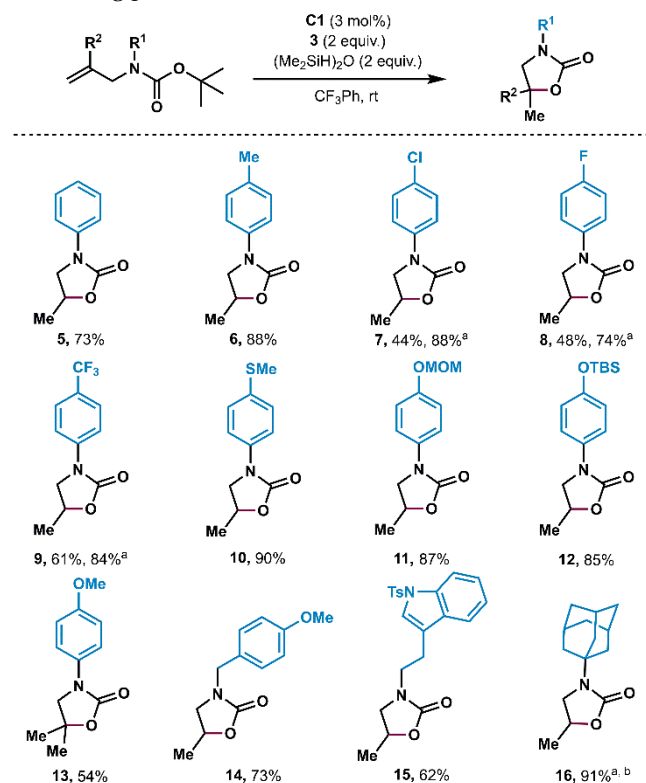
Encouraged by this result, we next examined the alkenyl carbamate scope for the formation of oxazolidinones (**Table 1**). Starting materials bearing hydrogen (i.e., **5**) or a methyl group (i.e., **6**) in the *p*-position of the aniline unit gave good yields of the desired products. On the other hand, the introduction of electron-withdrawing chloro, fluoro, and trifluoromethyl groups (**7–9**) led to significantly lower yields and the recovery of the alkenyl *tert*-butyl carbamate. Fortunately, we solved this problem by replacing the carbamate unit with a methyl group. Clearly, these results contrast with those from the reaction that produces **2** with the electron-donating methoxy group.

These aryl substituents would affect the rate of the intramolecular nucleophilic displacement and subsequent dealkylation, although their exact roles are not immediately clear. We also examined the functional group tolerance of this reaction using substrate **10** bearing a methylthio group, acid-sensitive acetal **11**, and fluoride-sensitive silyl ether **12**. The alkenyl *tert*-butylcarbamate bearing a disubstituted alkene, *p*-methoxybenzylamine, or *N*-tosyltryptamine cyclized to afford the desired products **13–15**. Moreover, amantadine derivative **16** was synthesized from the corresponding methyl carbamate on the 5-mmol scale. The corresponding *tert*-butyl carbamate was not as efficiently synthesized as the methyl carbamate (See SI).

We found that this method was able to form rings other than six-membered. Various cyclic carbamates **17–19** were prepared using the same reaction conditions from *tert*-butyl carbamates bearing *p*-methoxyaniline units (**Table 2**). To our great delight, these yields were improved by replacing the catalyst with **C2**, which was previously developed for the formation of medium rings by our group.[4a] Unfortunately, the yield of **19** was unsatisfactory. The methyl carbamate bearing the *p*-choroaniline unit and the *tert*-butyl carbamate bearing the *p*-methoxybenzylamine unit afforded the six-membered ring products **20** and **22** in good yields. However, we found that **21** and **23** were synthesized inefficiently using this method, even though **C2** was used.

We next applied the same concept to the preparation of cyclic ureas from alkenyl isoureas. Alkenyl *N*-tosyl-*O*-methylisoureas were synthesized from secondary amines in three steps (see SI). We found that the *p*-toluenesulfonyl group was required to produce cyclic ureas. Irrespective of the electronic character of the substituent on the aniline unit, the yields of imidazolidinones **24–29** were generally good to excellent (**Table 3**). Alkenyl isoureas bearing a disubstitued alkene or a *p*-methoxybenzylamine unit were also cyclized efficiently to give **30** and **31**. Six- and seven-membered cyclic ureas **32** and **33** were also prepared by this method in

good yields. A complex product mixture was formed and starting material was recovered in experiments aimed at forming eight-membered rings. We also investigated the cyclization of an alkenyl urea with the aim of potentially producing a cyclic urea.[14c] The cyclization of unpurified urea **35**, synthesized from *N*-allylaniline (**34**) and *p*-toluenesulfonyl isocyanate in ethanol, afforded cyclic isourea **36** (without **25**) in excellent yield from **34**. Therefore, it is clear that the dealkylative cyclization approach is valuable from the perspective of O/N selectivity.

With the aim of further extending synthetic utility, the *p*-toluenesulfonyl group in the product needed to be removable under mild conditions; however, we were unable to remove this group from **38** under common reaction conditions (**Scheme 3**). This observation prompted us to replace the *p*-toluenesulfonyl group with other groups, such as *o*-nitrobenzenesulfonyl and trifluoroacetyl. The yields of the cyclized products from **39** and **41** were acceptable and these transformations were scalable (1.00 g). Both protecting groups were removed to afford the same product **43** under mild conditions. In a preliminary attempt, the same reaction conditions were applied to the cyclization of alkenyl phosphoramidate **44**.

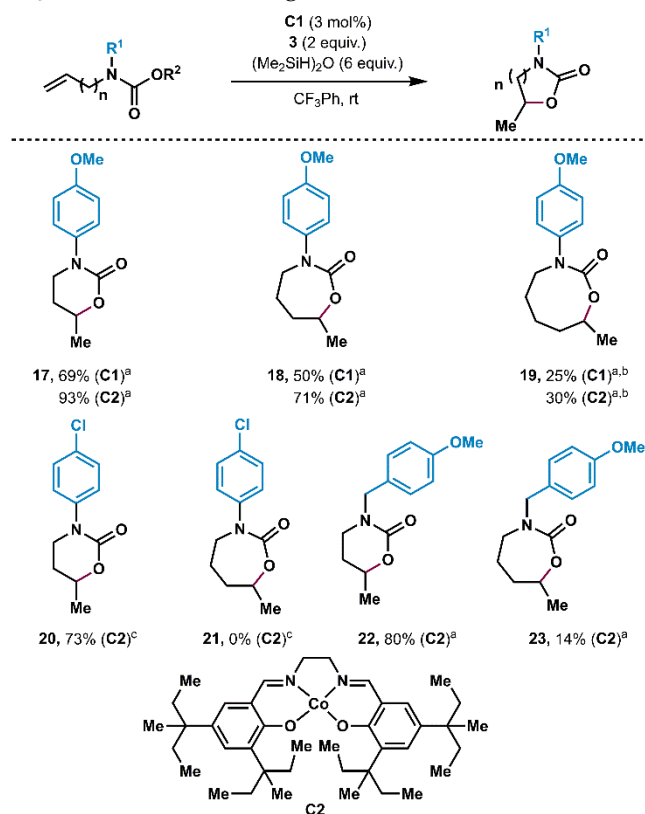**Table 1.** Scope of alkenyl carbamates affording 5 membered ring products

Conditions: alkenyl carbamate (0.2 mmol), **C1** (3 mol%), **3** (2 equiv.), 1,1,3,3-tetramethyldisiloxane (2 equiv.), benzotrifluoride (2.0 mL), room temperature, 18 h. [a]Methyl carbamate was used instead. [b]1.25 g (5 mmol) of starting material was used.

Table 2. Scope of alkenyl carbamates affording product of 6, 7, and 8 membered rings
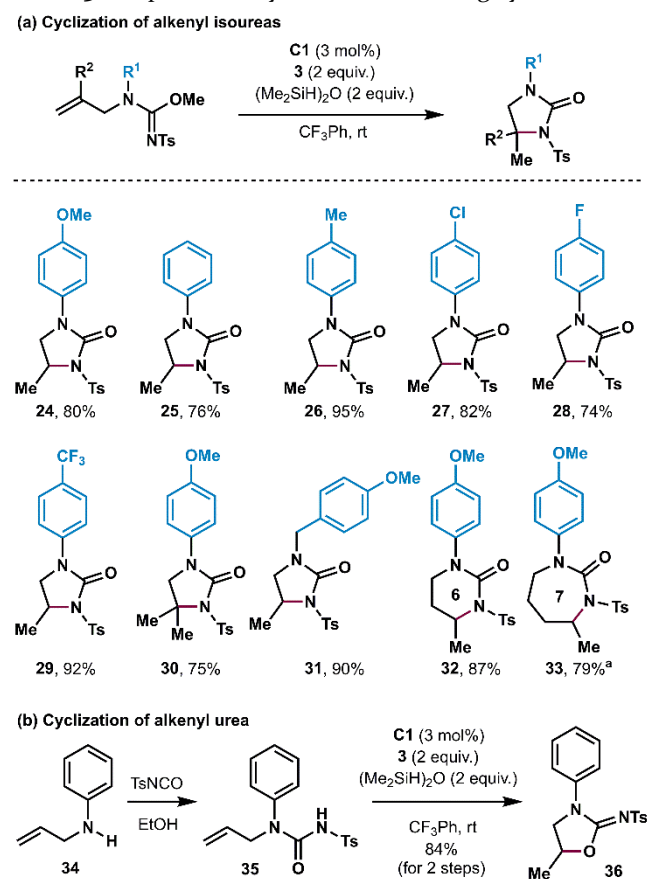

Conditions: alkenyl carbamate (0.2 mmol), **C1** (3 mol%), **3** (2 equiv.), 1,1,3,3-tetramethyldisiloxane (2 equiv.), benzotrifluoride (2.0 mL), room temperature, 18 h. [a]*tert*-Butyl carbamate was used instead. [b]**C2** was used. [c]Methyl carbamate was used.

Although there is much room for improving both yield and selectivity, we obtained the cyclic phosphoramidate **45**, together with a complex product mixture.

In summary, we developed a catalytic, Markovnikov-selective, functional-group tolerant, scalable method for the synthesis of cyclic carbamates using a TM-HAT/RPC approach. This reaction proceeds through the cyclization of an alkylcobalt(IV) intermediate and dealkylation by 2,4,6-collidine, and the mechanism was determined to be reasonable by DFT calculations. Various cyclic carbamates were efficiently synthesized under mild condition. Cyclic ureas and a cyclic phosphoramidate were also synthesized in the same way. The HAT-initiated reaction developed here enables the construction of medium ring carbamates and ureas. We are currently investigating enantioselective versions of these dealkylative cyclizations using a chiral cobalt catalyst.

Table 3. Scope of alkenyl isoureas affording cyclic ureas.

(a) Conditions: alkenyl carbamate (0.2 mmol), **C1** (3 mol%), **3** (2 equiv.), 1,1,3,3-tetramethyldisiloxane (2 equiv.), benzotrifluoride (2.0 mL), room temperature, 18 hours. [a]**C2** was used instead.

ASSOCIATED CONTENT

Experimental procedures and analytical data (^{1}H and ^{13}C NMR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Scheme 3. Additional experiment for cyclic urea synthesis
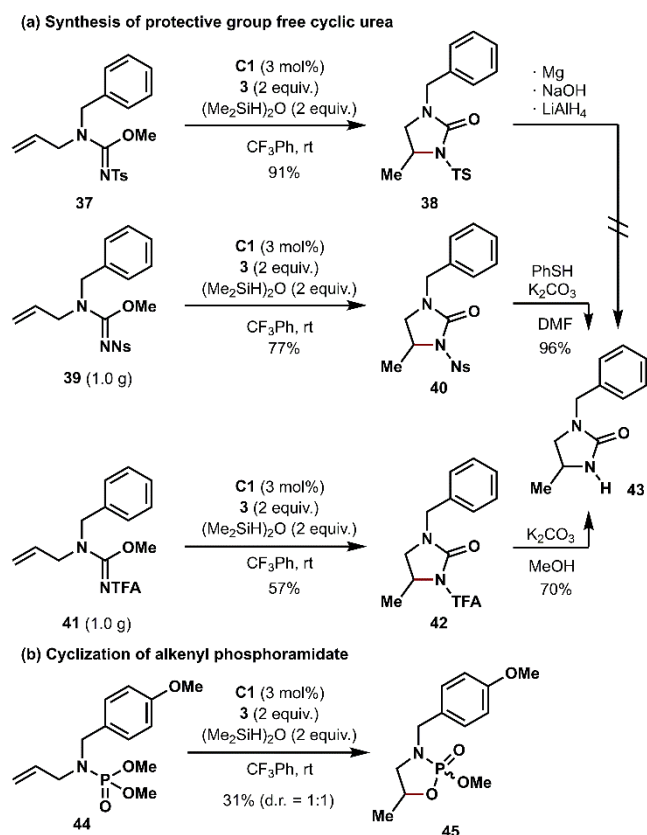
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TM-HAT & *RPC*

√ **functional-group tolerant** √ **5 − 8 membered ring** √ **Scalable**