Carbonylative C-C Bond Activation of Aminocyclopropanes Using a Temporary Directing Group Strategy

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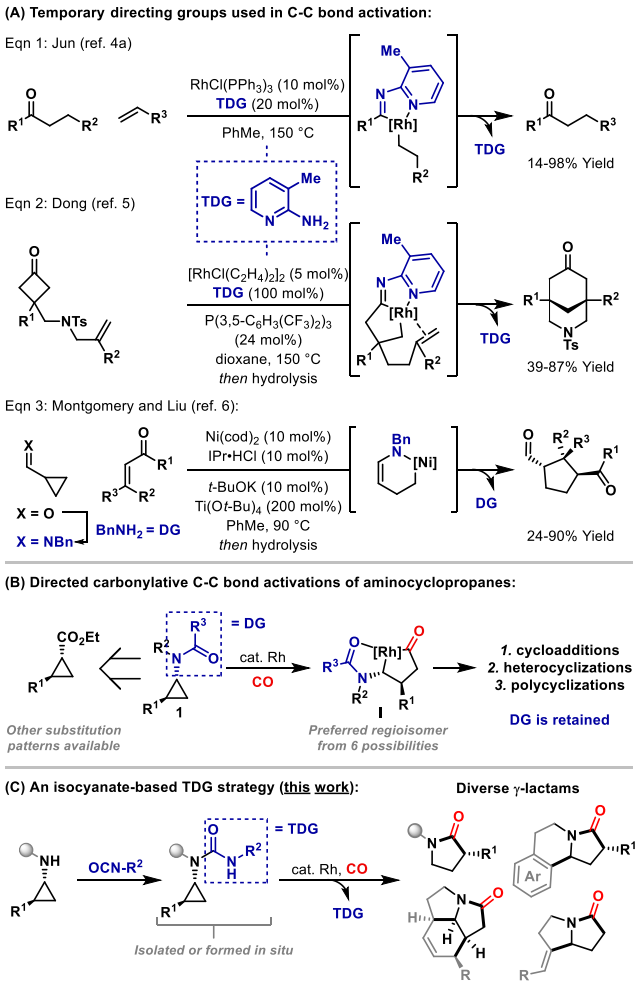
Supporting Information Placeholder

ABSTRACT: Temporary directing groups (TDGs) underpin a range of C-C bond activation methodologies; however, the use of TDGs for the regiocontrolled activation of cyclopropane C-C bonds is underdeveloped. In this report, we show how an unusual ring contraction process can be harnessed for TDG-based carbonylative C-C bond activations of cyclopropanes. The method involves the transient installation of an isocyanate-derived TDG, rather than relying on carbonyl condensation events as used in previous TDG-enabled C-C bond activations.

Methods based on catalytic C-C bond activation commonly require directing groups (DGs) to accelerate the rate and control the regioselectivity of metal insertion.[1] "Permanent" directing groups have been used to facilitate the activation of a relatively broad range of C-C bonds.[2] "Temporary" (or "transient")[3] directing groups (TDGs) are potentially more powerful because they can avoid the need for discrete DG installation and removal steps. Jun's seminal work achieved activations of ketone-based substrates via condensation with 2-amino-3-picoline to generate the corresponding imines (Scheme 1A, Eqn. 1), and this strategy has been developed significantly by Dong and co-workers.[4] Of particular relevance are examples involving 4-membered ring systems, specifically those based on cyclobutanones (Eqn. 2).[5] By contrast, the use of TDGs for the activation of 3-membered carbocycles (e.g. cyclopropanes) is virtually unknown. Perhaps the closest precedent is Montgomery's use of cyclopropanal-derived imines in Ni-catalyzed (3+2) cycloadditions (Eqn. 3);[6] here, discrete steps were required for DG installation and removal, although there is evident potential for refinement to a "full" TDG-based protocol. An impediment in this area is that, until recently, most C-C bond activation methodologies involving 3-membered carbocycles required highly activated or specialized variants (e.g. spirocyclopropanes, cyclopropenes, alkylidene cyclopropanes)[1b] that are not easily adapted to TDG-based settings.

Efforts in our laboratory have focused on the development of C-C bond activations of less activated 3-membered carbocycles.[7] There are significant benefits to such an approach because "simple" cyclopropanes are easy to access with a range of substitution patterns and in enantiopure form. Consequently, in principle, they can function as "spring loaded" initiating motifs for the stereospecific installation of 3-carbon units. However, the realization of such processes is hampered by (a) controlling the regioselectivity of C-C bond activation and (b) the instability of the incipient metallacyclobutane, which is prone to deleterious β-hydride elimination.[8] To address these issues, we have developed DG controlled carbonylative processes, where tractable rhodacyclopentanones[9] **I** are

Scheme 1.



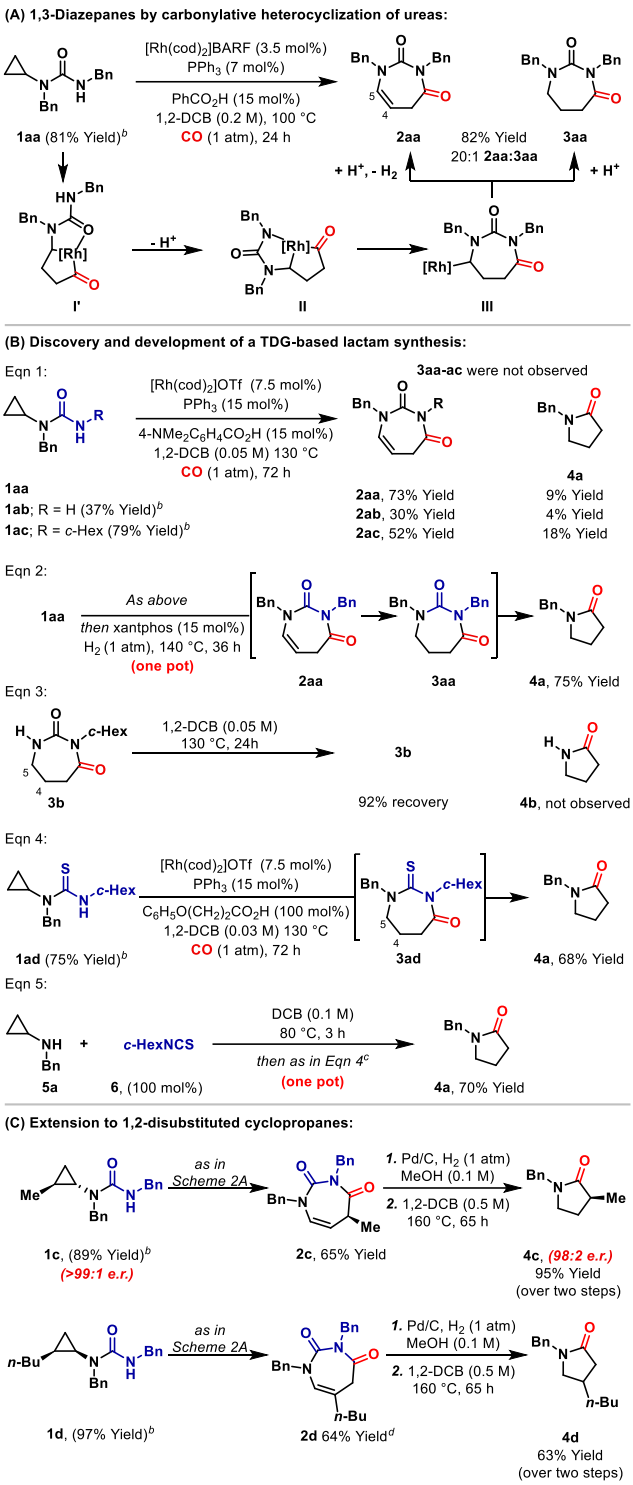
generated from aminocyclopropanes[10] **1** (and related species) with very high levels of regiocontrol (Scheme 1B).[7] Using this approach, a variety of multicomponent cycloadditions,[11] heterocyclizations[12] and polycyclizations[13] have been achieved. A key feature of our processes is the use of an N-carbonyl-based directing group, which either becomes part of the new ring system, or, in some cases (e.g. N-Cbz), can be removed after the C-C bond activation process. On first inspection, none of our previous processes are easily extended to a TDG-based scenario; however, in this report, we show how this can be achieved by exploiting an unusual ring contraction. The method, which involves the installation and subsequent expulsion of an isocyanate-derived TDG, provides diverse γ-lactams and offers a unique framework for developing TDG-based C-C bond activations (Scheme 1C).

We have previously shown that carbonylative heterocyclization of **1aa** delivers **2aa** and **3aa** in a 20:1 ratio at 100 °C (Scheme 2A).[12a] In this process, the initially generated rhodacyclopentanone **I'** is converted to **II** in advance of C-N bond forming reductive elimination, which provides **III**. From here, **2aa** and **3aa** are generated by β-hydride elimination and protodemetallation respectively. When this reaction was conducted at 130 °C under slightly modified conditions, **3aa** was not observed, and lactam **4a** formed instead, along with expected product **2aa** (1:8 ratio) (Scheme 2B, Eqn. 1).[14] Re-exposure of **2aa** to the reaction conditions led only to decomposition and lactam **4a** was not formed. However, when the alkene unit of **2aa** was reduced by hydrogenation of the crude heterocyclization mixture, which was achieved in one pot by addition of H_2 (1 atm) and xantphos (15 mol%) and heating at 140 °C, lactam **4a** could be isolated in 75% yield (Eqn. 2). Because hydrogenation of **2aa** did not occur at lower temperatures, we were unable to halt the process at the stage of **3aa**. Nevertheless, the collective observations (as well as those described later) suggest that lactam **4a** originates from **3aa** and not **2aa**. Interestingly, NH-system **3b**, which is easy to access with C4-C5 saturation,[12a] did not undergo ring contraction upon heating (Eqn. 3).[15]

To improve the overall efficacy of the process, we sought carbonylation conditions that would generate directly C4-C5 saturated systems (cf. **3aa**) and so allow the direct formation of **4a**. Variation of the R group offered partial success; switching this from Bn to *c*-Hex improved the yield and selectivity for lactam **4a** (Eqn. 1). The most pronounced improvement was achieved by instead employing thiourea **1ad**, which led directly to lactam **4a** in 68% yield (Eqn. 4); here, the C4-C5 unsaturated variant of **3ad** was not observed. The thiourea unit can be installed *in situ* by reaction of cyclopropylamine **5a** with isothiocyanate **6** and direct exposure of the resulting mixture to the carbonylation conditions provided lactam **4a** in 70% yield (Eqn. 5). Thus, the directing group is installed and disappears in the same pot. Extension of the ring contraction to more heavily substituted cyclopropanes **1c** and **1d** was challenging because we were unable to identify conditions that avoided the predominant generation of the C4-C5 unsaturated product (Scheme 2C). Thus, we isolated alkenes **2c** and **2d**, which were formed efficiently from cyclopropanes **1c** and **1d**, and reduced them (Pd/C, H_2)[16] prior to thermally promoted ring contraction, which provided α- and β-substituted lactams **4c** and **4d**. In the former case, complete transfer of enantiopurity was observed, such that the challenging α-methyl stereocenter of **4c** was installed in 98:2 e.r. The regiochemical outcomes for the conversions of **1c** to **2c** and **1d** to **2d** have been rationalized in our earlier work.[12a] Further refinement of these processes can be envisaged, but, as outlined later, we instead opted to explore more ambitious applications of this TDG strategy. The use of thiourea analogues of **1c** and **1d** was investigated but heterocyclization occurred in low yield and regiocontrol for C-C bond activation was incomplete.

The ring contraction of **3** to **4** is unusual, and we are not aware of any examples that have been interrogated mechanistically.[17] Accordingly, we performed DFT analysis of the current process using simplified system **3a'** (Figure 1). These studies revealed an energetically feasible concerted pathway which results in expulsion of methyl isocyanate via attack of N6 onto C2 and concomitant cleavage of the C2-N1 bond ($\Delta G^{\ddagger}$ = 33.5 kcal mol^{-1}). A more

Scheme 2. Reaction discovery and development.[a]



[a] The following numbering system is used here and throughout: **1** = cyclopropyl (thio)urea, **2** = C4-C5 unsaturated diazepane, **3** = C4-C5 saturated diazepane, **4** = lactam, **5** = cyclopropylamine precursor, 1st letter = structural variant w.r.t the cyclopropylamine unit, 2nd letter = structural variant w.r.t the urea/thiourea unit. [b] Yield for urea/thiourea formation (see the SI); [c] $C_6H_5OCH_2CO_2H$ (200 mol%) was used. [d] Traces of regioisomer (< 10%) derived from C-C bond activation of the less hindered proximal C-C bond of **1d** were also observed.

conventional stepwise addition-elimination mechanism (proceeding via a tetrahedral intermediate) was found to be energetically unfeasible (see the SI). The concerted nature of the ring contraction process is similar to recently reported ring contractions of cyclicN-carboxyanhydrides.[18] In the current process, the nucleophilicity of the N6 center is key: ring contraction of unsaturated system **2a'**, where cross-conjugation with the alkene likely diminishes the nucleophilicity of the nitrogen lone pair, has a higher energy barrier ($\Delta G^{\ddagger}$ = 39.7 kcal mol^{-1}). This result is consistent with the observation that **2aa** does not undergo ring contraction to *dehydro*-**4a** (or **4a**).[15]

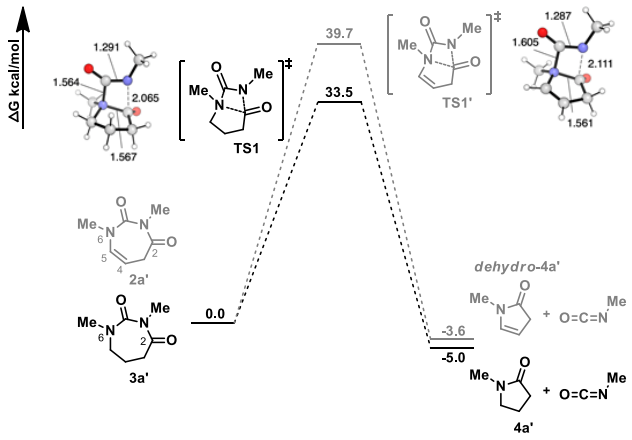


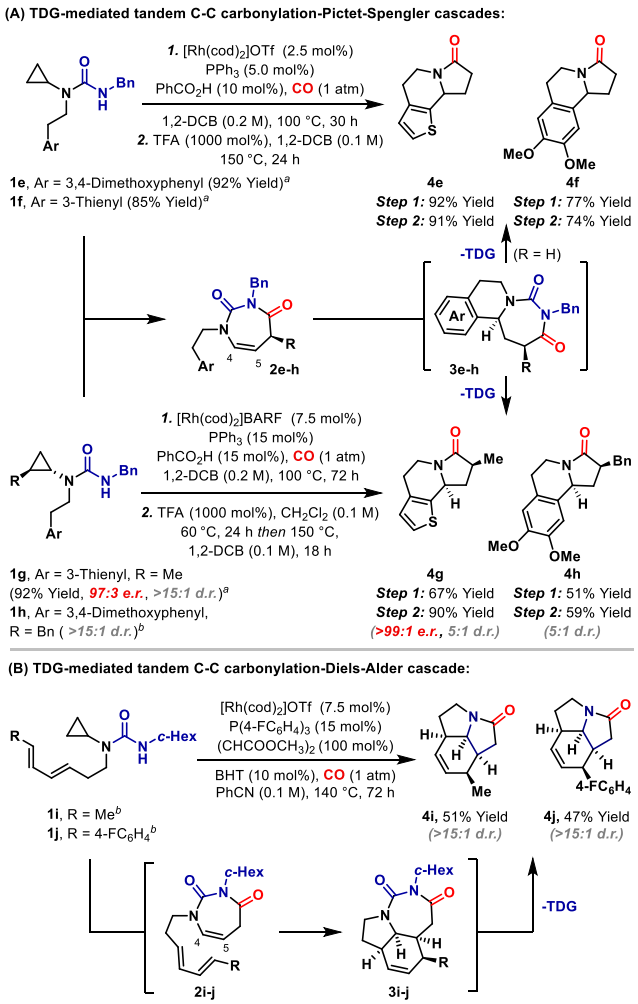
Figure 1. Free energy profiles computed at SMD(DCB)-DLPNO-CCSD(T)/def2-TZVPP//PBE0-D3BJ/def2-TZVP, 423.15 K. 3D geometries with key distances are quoted in Å.

The studies outlined so far show that ring contraction only occurs for diazepanes that possess C4-C5 saturation. Accordingly, we envisaged designing processes that exploit removal of the easily installed C4-C5 unsaturation in further bond formations. To this end, ureas **1e** and **1f** were exposed to carbonylative heterocyclization conditions, which generated **2e** and **2f** in 92% and 77% yield, respectively (Scheme 3A). Exposure of these products to TFA at high temperature effected Pictet-Spengler like cyclization which removed the C4-C5 unsaturation and triggered ring contraction to tricyclic lactams **4e** and **4f**. A one pot procedure was also investigated, wherein TFA was added directly after complete consumption of **1e/f**; this method provided **4e** and **4f** in 70% and 37% yield, respectively, without the need for isolation of **2e/f**. The protocol extended to disubstituted cyclopropanes **1g** and **1h** which provided targets **4g** and **4h** with good levels of diastereo- and regiocontrol. In the case of **1g**, complete transfer of enantiopurity was observed.[19]

Other types of tandem process are also possible. For example, carbonylative heterocyclization of dienyl systems **1i** and **1j** at 140 °C provided synthetically challenging tricyclic systems **4i** and **4j** in 51% and 47% yield, respectively, and as single diastereomers (Scheme 3B). Here, initial Rh-catalyzed cyclization to **2i/j** is likely followed by thermally promoted inverse electron demand Diels-Alder cycloaddition which provides adducts **3i** and **3j**. At this stage, the C4-C5 unsaturation present in **2i/j** is removed and so ring contraction can occur spontaneously to provide the target. For these processes, the inclusion of dimethyl fumarate (rather than a carboxylic acid additive) was found to be optimal.[11b] Additionally, BHT was employed as an additive to suppress radical polymerization of the diene substrate during the reaction.[20]

To extend the scope of the TDG strategy further, we sought processes where the initial formation of C4-C5 unsaturated

Scheme 3. TDG-mediated tandem C-C carbonylation processes.

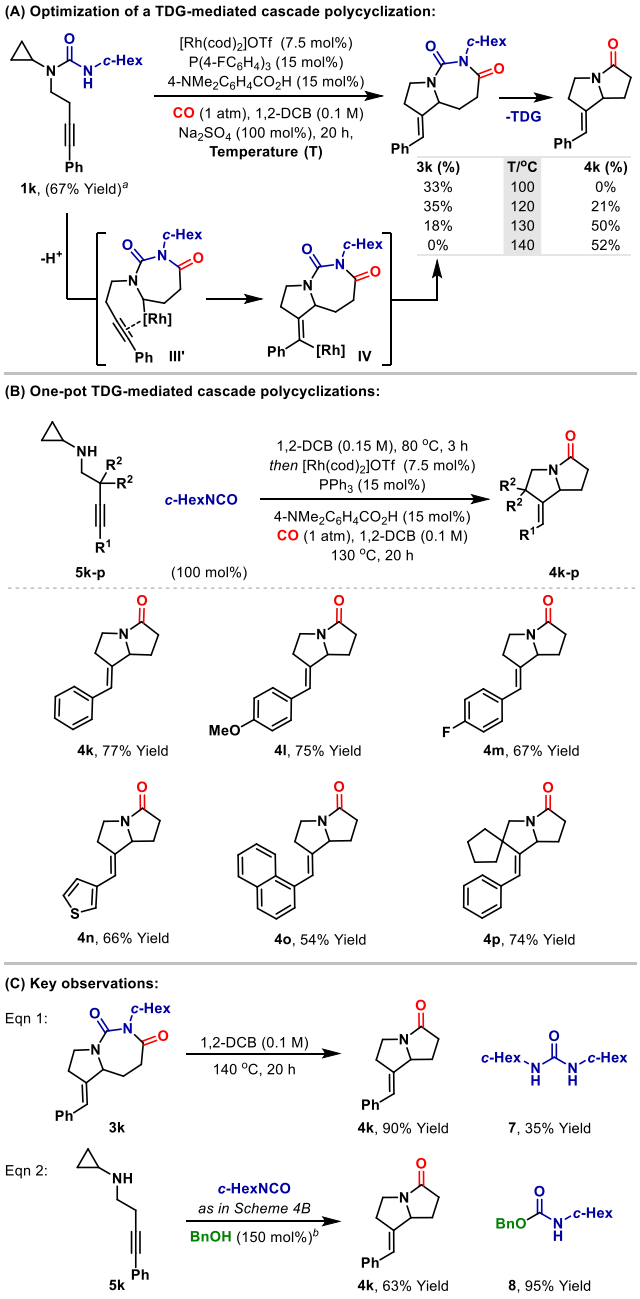


[a] Yield for urea formation (see the SI); [b] A yield for the installation of the urea unit was not obtained as this substrate was synthesized using in a one-pot multistep procedure.

products might be avoided by harnessing the alkyl-Rh(I) intermediate (cf. **III**, Scheme 2A) in further bond formations. To this end, we examined carbonylative cyclization of **1k** – in this system, the initially generated alkyl-Rh(I) species **III'** undergoes *syn*-stereospecific carbometallation of the pendant alkyne prior to protodemetallation to provide **3k** (Scheme 4A).[13] Accordingly, the rhodacyclopentanone functions as an ambiphilic unit, with its electrophilicity promoting the first cyclization and the nucleophilicity of the ensuing alkyl-Rh(I) species **III'** facilitating the second.

When the reaction was run at 100 °C only diazepane **3k** was observed. However, as the temperature was increased to 140 °C, lactam **4k** was isolated as the sole product, thereby confirming the requirement for elevated temperatures for the ring contraction process. The protocol could be extended to a "full" TDG setting by premixing amine **5k** with cyclohexyl isocyanate prior to addition of the components required for the carbonylative heterocyclization/ring contraction sequence (Scheme 4B). Using this method, and by switching the ligand from $P(4\text{-}FC_6H_4)_3$ to PPh_3, adduct **4k** was formed in 77% yield. The protocol extended to a range of different alkynes which provided targets **4l-p** in 54-77% yield. To corroborate the mechanism of these processes, diazepane **3k** was isolated and heated at 140 °C, which, as expected, effected ring contraction to **4k** (90% yield, Scheme 4C, Eqn. 1). Here, we were also able to isolate urea **7**, a byproduct that is consistent with release of cyclohexyl isocyanate during ring contraction.[21] To add further support to this, the optimized protocol for the conversion of **5k** to **4k** was run in the presence of benzyl alcohol (Eqn. 2). This led to the isolation of carbamate **8** in 95% yield, a result that is also consistent with the release of cyclohexyl isocyanate.

Scheme 4. TDG-mediated tandem C-C carbonylation cascades and key observations.



[a] Yield for urea formation (see the SI); [b] BnOH was added with the Rh-catalyst.

In summary, we demonstrate that readily available iso(thio)cyanates can function as temporary directing groups in carbonylative C-C bond activations of aminocyclopropanes. In so doing, this reactivity manifold now extends, for the first time, to the direct preparation of complex γ-lactams, including variants bearing stereodefined substituents. The chemistry is underpinned by an unusual ring contraction process, and, through understanding key mechanistic features of this, tandem and cascade processes have been developed that exploit either classical reactivity or the ambiphilic nature of the key rhodacyclopentanone intermediates. In broader terms, these studies validate a conceptually unique TDG-based strategy for C-C bond activation. Specifically, the processes are the first in this area that do not harness carbonyl condensation and imine hydrolysis for TDG installation and removal.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest

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(14) A wide range of acid additives were screened to improve the ratio of **2aa:3aa** and thereby facilitate ring contraction. From these studies, 4-$NMe_2C_6H_4CO_2H$ emerged as the optimal choice. When the conditions in Eqn. 1 were used at 100 °C **2aa** and **3aa** formed in 68% and 6% yield, respectively, and **4a** was not observed (cf. Scheme 2A).

(15) The SI outlines DFT studies on a simplified system related to **3b** that are analogous to those in Figure 1. These indicate that the barrier for ring contraction in this case ($\Delta G^{\ddagger}$ = 38.4 kcal mol^{-1}) is higher than for **3a'**. This is tentatively attributed to the lower nucleophilicity of the NH vs N-alkyl center. Under basic conditions, **3b** does undergo ring contraction; DFT studies indicate a stepwise mechanism is operative in this case.

(16) The crude reduction product was characterized by ^{1}H NMR spectroscopy (see the SI).

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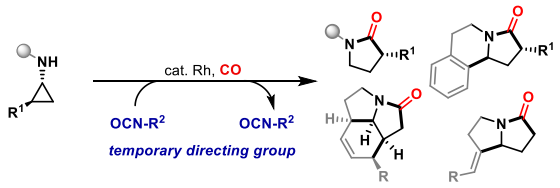
(19) For these processes, the TFA promoted cyclization step was conducted at 60 °C (vs 150 °C for **1e** and **1f**) prior to heating at 150 °C for the ring contraction. This modification enhanced diastereoselectivity, because this aspect is controlled by the TFA-promoted step. When the TFA promoted cyclization was conducted at 150 °C in 1,2-DCB, **4g** was formed in 2.6:1 d.r. The optimized conditions employ a solvent switch from CH_2Cl_2 to 1,2-DCB. When 1,2-DCB was used for both steps, **4g** was formed with lower diastereoselectivity (4:1 d.r. vs 5:1 d.r. under optimized conditions).

(20) In the absence of BHT, the processes in Scheme 3B give <40% yield. For the use of BHT in C-C bond activation processes, see: Murakami, M.; Itahashi, T.; Ito, Y. Catalyzed Intramolecular Olefin Insertion into a Carbon−Carbon Single Bond. *J. Am. Chem. Soc.* **2002**, *124*, 13976.

(21) A plausible pathway involves hydration of *c*-HexNCO (by adventitious water) in advance of decarboxylation to *c*-$HexNH_2$. This can then react with a second equivalent of *c*-HexNCO to deliver **8**.


NH
R1
cat. Rh, CO
OCN-R2
OCN-R2
temporary directing group
O
N
R1
H
R