C–H Insertion

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Remote C–H Functionalization: Using the N–O Moiety as an Atom-Economical Tether to Obtain 1,5- and the Rare 1,7-C–H Insertions**

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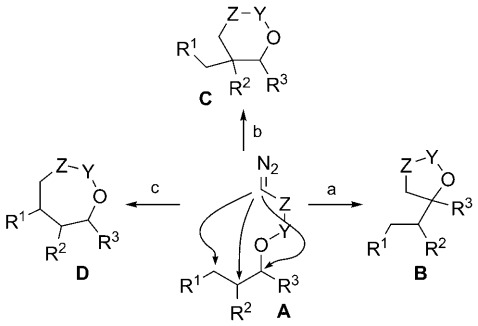
Contemporary organic synthesis faces the demands of improving its efficiency[1] by redox and atom economy, including achieving superior chemo-, regio-, and stereoselectivity.[2] Consequently, there has been great interest in the transformations of inert C–H bonds, as these open up new avenues in synthesis. Significant progress has been made towards site-selective C–H-insertion reactions,[3] but this field still presents major challenges[4] owing to the ubiquitous nature of C–H bonds in organic molecules. The regioselectivity of C–H insertions is governed by electronic, steric, and conformational factors.[5] In non-constrained systems, intramolecular C–H-insertion reactions predominately afford five-membered rings. Three, four, six, and rarely higher-membered rings[6] can only be obtained by intramolecular C–H insertion if the system is specially constrained,[7] contains special moieties,[8,9] or if the C–H bond is activated by a heteroatom.[6a,10] Thus far, not many systems have been shown to afford rings larger than five-membered rings without the need to bias the system. The discovery of new rules and tethers that facilitate the construction of bigger ring sizes by C–H insertion will enable the remote functionalization of complex molecules.

Tethering reacting partners together can lead to better regio- and stereoselectivities, but this selectivity can be negated if the tether is difficult to remove or transform into other moieties. New tethers that can either be readily transformed into other functionalities or do not limit C–H insertion to specific ring sizes are highly desirable. Herein, we identify N-alkoxy-N-alkyl amides as atom-economical tethers for C–H-insertion reactions to give amino-hydroxy functionalized systems.[11,12] We demonstrate, using both computational and experimental methods, that this tether facilitates remote C–H functionalization reactions, and that the C–H insertion site selectivity using this particular tether can be modulated by the reaction conditions and/or the electronics of the ligand of the dirhodium catalyst.

The use of the nitro group to introduce amino-hydroxy groups into complex molecules through different stereoselective strategies has been elegantly demonstrated by the Denmark group and others.[13] Along this line, we reasoned that C–H-insertion reactions using an N–O tether that is obtained from the transformation of a chiral heteroatom could be a simple way to stereoselectively introduce amino-alcohol functionality into complex molecules.[14] The N–O moiety is a perfect atom-economical tether because several mild methods are available for the facile cleavage of the N–O bond with complete retention of the atoms that constitute the tether. Thus far, the use of an N–O tether to direct C–C bond formation through carbenoid insertion is under-developed.[15] N–O-tethered intramolecular C–H insertion via an entropically favorable six-membered transition state (TS) would enable insertion alpha to the oxygen atom to give compound **B** whereas compound **C** would be obtained by insertion into the C–H bond, which is beta to the oxygen atom in diazo substrate **A** (Scheme 1).[6a] Because enantiopure secondary alcohols can be readily obtained using a myriad of methods, such as the asymmetric reduction of ketones,[16] difficult-to-obtain enantiopure tertiary alcohols can be accessed after N–O cleavage.

Conversely, N–O-tethered intramolecular C–H insertion via an eight-membered TS to give seven-membered ring products would enable the functionalization of a remote center using an existing heteroatom moiety (compound **D**, Scheme 1). A challenge in using amide tethers in C–H-insertion reactions to obtain remote functionalized products is to design strategies that can bias the conformer equilibrium to achieve site-specific functionalization (**A1** or **A2**; Scheme 2). For N-alkoxy-N-alkyl diazo compounds, the conformation whereby the alkoxy moiety is positioned *trans* to the carbonyl functionality (**A1**; Scheme 2) is at least



Scheme 1. Remote C–H functionalization using an atom-economical tether.

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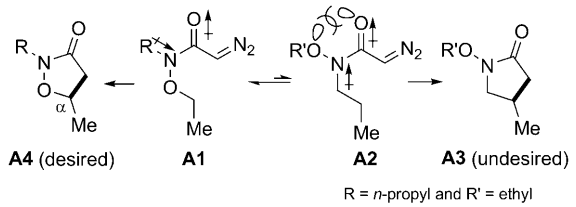
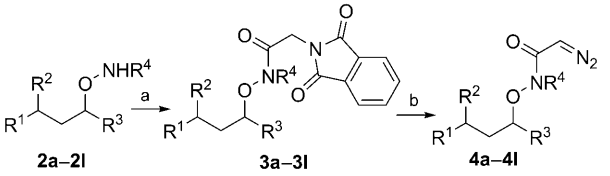


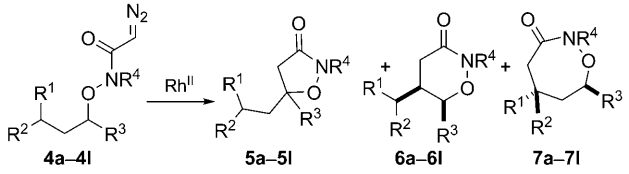
Scheme 2. Conformational equilibrium in acyldiazo systems.

5 kcal mol^{-1} more stable than the conformer which has both the carbonyl and alkoxy moieties *cis* to each other (**A2**; Scheme 2 and Figure 1).[17] Increasing the steric bulk of the N-alkyl group does not change the conformational ratio of **A1** to **A2**, in contrast to the well-studied diazoamides in which more bulky N-alkyl substituents prefer to be *cis* to the carbonyl moiety to avoid unfavorable 1,3-allylic strain.[18]

Two unfavorable factors, lone pair–lone pair repulsion and re-enforcing dipole moments (**A2**; Scheme 2), probably account for the lower stability of the *cis* conformer (compare the energy levels of **S10** + **X** and **S1** + **X**, Figure 1). The rate-determining step for the C–H insertion depends upon nitrogen extrusion (Figure 1 and Ref. [5d]). Calculations at the B3LYP/631GLAN level reveal that nitrogen extrusion from the complex of the rhodium catalyst and the N-alkoxy diazoamide is more facile (by 3.4 kcal mol^{-1}) when the N-alkoxy moiety is *trans* to the carbonyl group than when the group is *cis* to the carbonyl group (Figure 1 and the Supporting Information). Together, these factors favor C–H insertion at the position α to the oxygen atom (**S6**) over the alternative product (**S15**, Figure 1; for detailed analysis, see the Supporting Information). The preparation of diazoalkoxyamide substrates **4a–l** for regioselective C–H insertion was straightforward (Scheme 3). With a range of N-alkoxy-N-alkyl diazoamides in hand (**4a–4l**), we proceeded to investigate their intramolecular C–H-insertion reactions



Scheme 3. Synthesis of N-alkoxy-N-alkyl diazoamides **4a–4l**: a) Phthalylglycyl chloride, Et_3N, CH_2Cl_2, 0 °C, 5 h; b) hydrazine, ethanol, 40 °C, 4 h; then $NaNO_2$, H_2O, CH_2Cl_2, HCl or HOAc (pH 2–4), 0 °C, 2 h.



Scheme 4. [{Rh(OAc)$_2$}$_2$]-catalyzed reaction of substrates **4a–4l**.

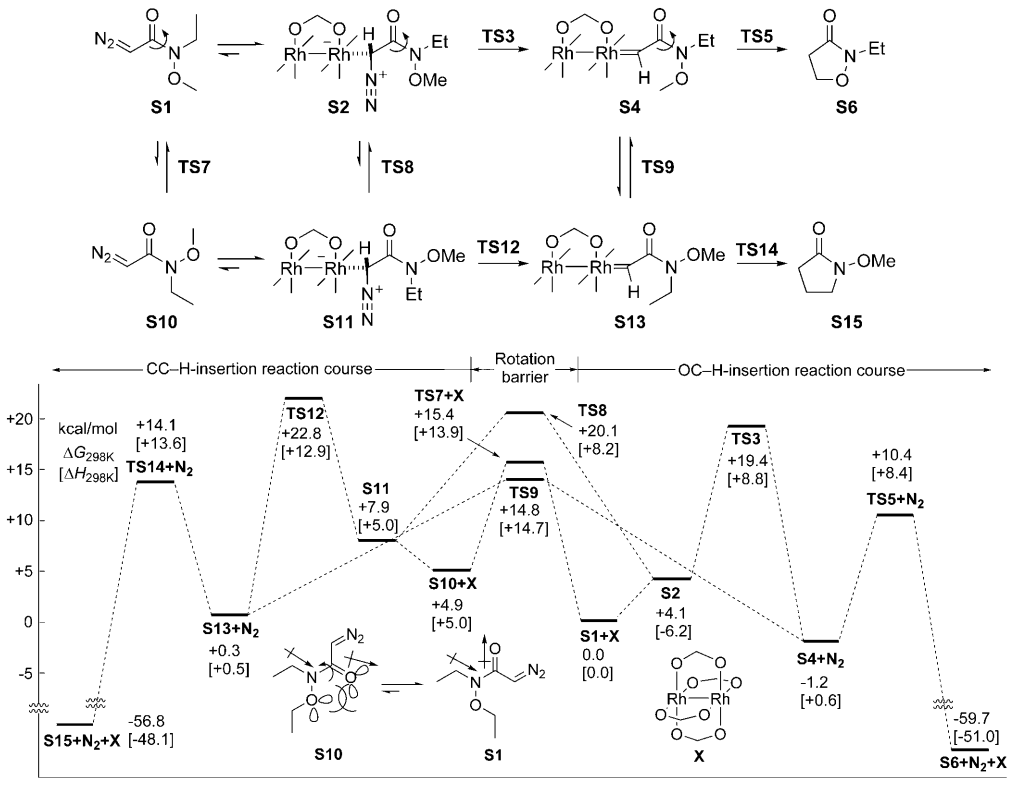


Figure 1. Reaction pathways and the potential surface of the C–H insertion model reaction at the B3LYP/631GLAN level. The simpler dirhodium catalyst **X** and substrate **S1** were used instead of dirhodium tetraacetate and more complex substrates to make the computation more manageable.

(Scheme 4). Preliminary results using **4c** as a model substrate showed that the 1,5-C–H insertion product was the major product with the 1,7-C–H insertion product as a minor product (Table 1, entry 1). Interestingly, the 1,6-C–H insertion product was not observed at all. Obtaining the unusual 1,7-C–H insertion product, albeit as a minor product, prompted us to investigate different reaction conditions and substrate substitution patterns that might increase the ratio of the 1,7-C–H insertion product (**7c**). Temperature seems to only have a minor effect on the product distribution of N-alkoxy-N-alkyl diazoamide C–H-insertion reactions; higher temperatures marginally favor the 1,5-C–H insertion product (cf.

Table 1: Screening of the Rh^{II}-catalyzed reaction of **4c**.

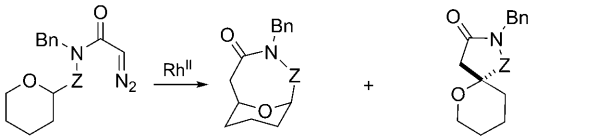
Entry	Catalyst[a]	*T* [°C]	Ratio **5**:**7**[b]
1	$[\{Rh(AcO)_2\}_2]$	−40	88:12
2	$[\{Rh(AcO)_2\}_2]$	0	90:10
3	$[\{Rh(AcO)_2\}_2]$	25	92:8
4	$[\{Rh(AcO)_2\}_2]$	40	94:6
5	$[\{Rh(AcO)_2\}_2]$	70[c]	96:4
6	$[\{Rh(CF_3CO_2)_2\}_2]$	40	64:36
7	$[(Rh\{CF_3(CF_2)_2CO_2\}_2)_2]$	40	60:40
8	$[\{Rh(heptylCO_2)_2\}_2]$THF	40	94:6
9	$[Rh_2(esp)_2]$	40	94:6
10	$[Ru_2(cymene)_2Cl_4]$	40	>99:1
11	$[Rh_2(cap)_4(CH_3CN)_2]$	40	>99:1

[a] Reactions were performed using 2 mol% of the catalyst, CH_2Cl_2, 2 hours. [b] Ratio based on HPLC and ^1H NMR spectroscopic analysis. [c] Reaction was performed in $ClCH_2CH_2Cl$. esp = rhodium (α, α, α′, α′-tetramethyl-1,3-benzenedipropionic acid, cap = caprolactamate.

Table 2: $[\{Rh(AcO)_2\}_2]$-catalyzed reactions of **4a**–**4l**.

4	$R^1(R^2)$	R^3	R^4	Total yield [%][a]	Ratio **5**/**7**[b]
a	Ph(H)	Me	Me	67	50:11[c]
b	Ph(H)	Me	Et	58	41:12[d]
c	Ph(H)	Me	*i*Pr	75	70:5
d	Ph(H)	Me	*i*Bu	64	51:13
e	Ph(H)	Me	Bn	80	59:21
f	Ph(H)	Me	Mes	83	58:25
g	Ph(H)	Me	4-MeOBn	77	62:15
h	Ph(H)	H	4-MeOBn	65	40:25
i	Ph(Me)	H	4-MeOBn	65	36:29
j	Me(H)	CO_2Et	Bn	53	5:48
k	Ph(H)	CO_2Et	Bn	54	0:54
l	Et(H)	Me	Bn	78	65:7[e]
l[f]	Et(H)	Me	Bn	61	37:14[g]

[a] Yield of isolated product. [b] Ratio based on the yields of pure isolated products. [c] 6% of six-membered analogue **6a** was isolated. [d] 5% of **6b** was isolated. [e] 6% of **6l** was isolated. [f] Catalyzed by 4 mol% $[\{Rh(CF_3CO_2)_2\}_2]$. [g] 10% of **6l** was isolated. Mes = mesityl.



Scheme 5. $[\{Rh(OAc)_2\}_2]$-catalyzed reaction of tetrahydro-2*H*-pyran-2-yl (**8a**) and tetrahydro-2*H*-pyran-2-yl-oxy (**8b**) diazo analogues. The reaction conditions are the same as those indicated in the Table 2. In the case of **8a**, a minor product that was derived from the Buchner reaction was observed; Bn = benzyl.

Table 1, entries 1–5). Conversely, the electronics of the rhodium ligand play a pivotal role in product distribution. Electrophilic carbenoids, generated from the electron-deficient $[\{Rh(CF_3CO_2)_2\}_2]$ or $[\{Rh[CF_3(CF_2)_2CO_2]_2\}_2]$ complexes, increase the propensity of the reaction to be channeled through the 1,7-C–H insertion reaction pathway whereas electron-rich $[Rh_2(cap)_4]$[19] promotes the exclusive formation of the 1,5-insertion product (see Table 1, entries 6, 7, and 11). Ruthenium-based catalysts, such as $[Ru_2(cymene)_2Cl_4]$, also afforded the 1,5-C–H insertion product almost exclusively (entry 10, Table 1).

We proceeded to investigate how the substitution pattern in the substrate affected the ratio of the 1,5- to 1,7-C–H insertion products when $[\{Rh(OAc)_2\}_2]$ was used as the catalyst. Compounds **4a**–**g** were designed to probe how the N-substituent affected product ratio. For most of the N substituents, 1,5- and 1,7- but not 1,6-insertion products were obtained. However, for smaller N-alkyl groups (methyl and ethyl groups, **4a** and **4b**, respectively), approximately 5% of the 1,6-insertion product was obtained. The amount of 1,7-insertion product increases when primary N–O tethers are used (compounds **4h** and **4i**), in line with the lower propensity for C–H insertion to occur at primary centers.[20] Compound **4l**, which lacks benzylic C–H bonds, afforded more 1,7- than 1,6-insertion product (albeit modestly).[21]

C–H insertions next to carbonyl groups are rare;[22] consequently, 1,7-insertion products can be predominately obtained when electron-withdrawing groups, such as esters, are positioned next to the N–O tether (**4j** and **4k**, Table 2). With **4j** and **4k**, the C–H insertions occurred next to methyl and phenyl groups, respectively. Interestingly, the 1,7-C–H insertion only occurred on the *si* face when R^3 = Me and R^2 = Ph (see the Supporting Information, Scheme S3) but was not stereoselective when $R^3 = CO_2R$ and R^2 = Me).

The use of conformational effects to direct remote C–H functionalization is illustrated with substrates **8a** and **8b**, which afford exclusively 1,5- and 1,7-C–H insertion products, respectively (Scheme 5). In **8b**, an axial anomeric N–O tether was expected to predominate over an equatorial N–O tether because of favorable interaction between the lone pairs of the endocyclic oxygen atom and the σ* of the anomeric C–O bond (**B8**, Figure 2). Also, favorable interaction between the lone pairs of the endocyclic oxygen atom and the σ* of the C–H_γ bond in **B8** would increase the hydridic character of H_γ

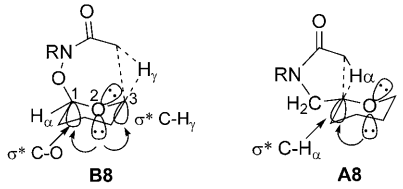
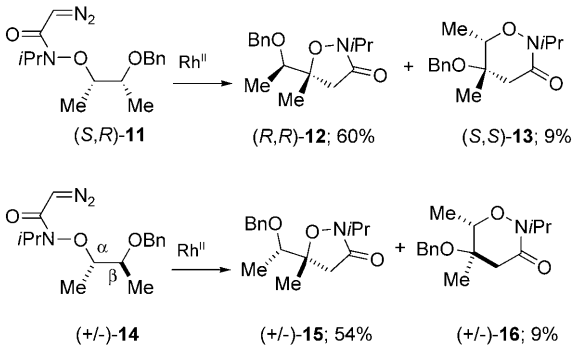


Figure 2. Formation of the 1,5- and 1,7-insertion products.

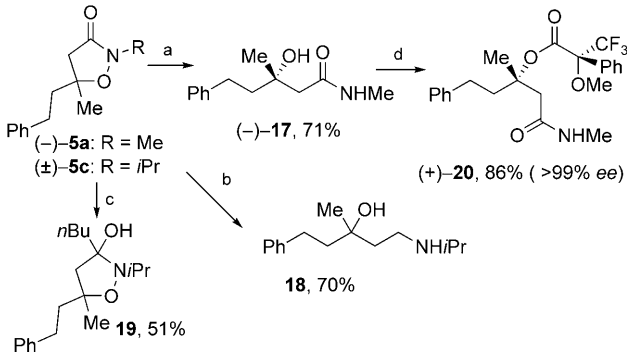
in **B8** and promote the formation of the 1,7-C–H insertion product. In contrast, the equatorial H_α in **B8** cannot be activated by the lone pairs on the endocyclic oxygen atom because of poor orbital overlap. In fact, H_α is deactivated by virtue of being next to an electron-withdrawing oxygen atom.[23] The transition state for the 1,7-insertion pathway in **B8** is probably stabilized by three-center–two-electron-like interactions (σ*C–O, p orbital, σ*C–H_γ). The low propensity to form six-membered rings with N–O-tethered diazo compounds is further demonstrated with compounds **11** and **14** (Scheme 6). In both compounds the β-C–H bonds are



Scheme 6. β-C–H bond activated substrates still predominantly afforded the α 1,5-insertion products.

activated by the oxygen atom,[24] but five-membered rings are predominantly obtained with both starting materials. Starting with enantiopure diastereomer **11**, single diastereomeric products **12** and **13** are obtained, which indicates that N–O tethered C–H-insertion reactions are stereospecific, in line with an earlier observation by Taber and co-workers.[25]

The N–O tether is a value-added tether because of its versatility in being transformed into several different functionalities that can be elaborated into diverse moieties. For example, treatment of compound **5** (R = *i*Pr; Scheme 7) with Red-Al in anhydrous tetrahydrofuran and toluene, and



Scheme 7. Transformations of **5a** and **5c**; synthesis of the tertiary alcohols: a) Raney-Ni, EtOH, 70 °C; b) Red-Al, THF/toluene (1:2), then zinc, AcOH/H_2O (9:2); c) *n*BuLi, toluene, −78 °C to 10 °C; d) (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, Et_3N, CH_2Cl_2, 40 °C. Red-Al = sodium bis(2-methoxyethoxy)aluminumhydride.

subsequent treatment with zinc dust, afforded tertiary alcohol **18** in 70 % yield. Importantly, the aminohydroxy moiety in **18**, in which the alcohol is tertiary, is common in several bioactive molecules. Also, the N–O moiety can be cleaved without sacrificing the carbonyl group. Treatment of enantiopure **5a** (R = Me, > 99 % *ee*) with Raney nickel gave enantiopure **17** (> 99 % *ee*, a non-aldol aldol product); confirming that deracemization does not occur in N–O-tethered C–H-insertion reactions. Enantioenriched aldol products from acetate derivatives (the acetate-aldol problem)[26] or asymmetric ketone-aldol reactions have traditionally been difficult to obtain using conventional aldol reactions. Therefore, the N–O-tethered C–H-insertion reaction, starting from readily available enantioenriched secondary alcohols could be an alternative solution to solving the acetate-aldol problem in asymmetric aldol methodologies. Also, the addition of a butyl nucleophile to the N–O-tethered C–H-insertion product **5** (R = *i*Pr) gave the hemi-aminal product **19**, without over addition to the keto functionality. Compound **19** can be further elaborated into diverse molecules by leveraging on the diverse transformations of the keto group.

In conclusion, we have demonstrated that the N–O tether is a versatile, atom-economical tether that facilitates remote C–H functionalization in organic molecules. Use of this tether to make complex molecules,[27] and further mechanistic studies[28] aimed at understanding N–O-tether-promoted regioselection are being pursued in our laboratory.

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