Atom-Economical Synthesis of Complex Heterocycles with N–O Moiety

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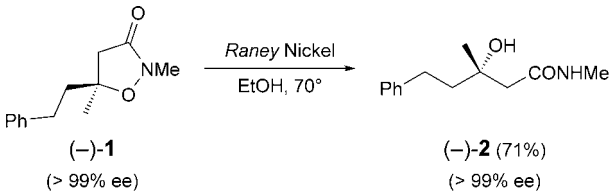
A concise and facile method for the synthesis of heterocyclic compounds with N–O tether was introduced. The two important steps of the synthesis are a *Mitsunobu* reaction and C–H activation. The *Mitsunobu* protocol allows to form the N–O moiety in the molecule, while subsequent C–H activation leads to heterocycles.

Introduction. – Construction of complex heterocycles [1–3] has been a particularly fruitful area of investigation, and the diazo functionality seems to be a versatile tool to synthesize those complex molecules. Recent advances have shown that the tether to the diazo moiety can impact selectivity in reactions. For example, *Du Bois* and *Novikov* showed that diazo sulfones/sulfates give unique six-membered rings, providing a useful way to functionalize C-atoms in γ-position to OH functionalities [4][5]. Cyclization of a metallocarbenoid intermediate generated from the diazo precursor is one of the most common methods. Recently, *Sintim*'s group reported a method which utilizes an N–O tether for the formation of cyclopropyl-fused pyrrolidines [6]. The N–O tether is a very practical tool to obtain aminoalcohols, as it can be easily cleaved under mild conditions and the atoms that consitute the tether remain.

The OH function is easy to install in molecules enantioselectively. Consequently, there have been numerous studies on the asymmetric synthesis of tertiary alcohols to further functionalize molecules, *e.g.*, *Sharpless* OH-directed epoxidation, *Donohoe* OH-directed dihydroxylation, *Simmons–Smith* OH-directed cyclopropanation [7], and asymmetric reduction of ketones [8]. However, catalytic asymmetric addition of C-nucleophiles to ketones might be challenging due to the poor electrophilic character of the ketone group (compared with aldehydes), and it is difficult to obtain enantiopure tertiary alcohols by this method, because the smaller steric and electronic differences between the two substituents of the ketone cause difficulty for the enantioface differentiation [9]. Facile N–O cleavage under mild conditions offers an easy method for the enantioselective synthesis of tertiary alcohols (*Scheme 1*) [10]. For example, treatment of enantiopure (–)-**1** with *Raney* nickel yielded enantiopure (–)-**2**. This method could be an alternative and better method to obtain enantiorich aldol products.

There are also pharmaceutically active molecules that contain the N–O tether: the alkaloid geneserine which is used for adjuvant treatment of dypepsia [11], the dioxopiperazine antibiotic gliovirine and FA-2097 [12], and methylbenzoxazinones which are nuclear hormone receptors for binding glucocorticoid [13] are examples of N–O tether-containing drugs.

Scheme 1



Since modern organic synthesis should be atom-economic with the goal of chemo- and regioselectivitiy, transformation of inert C–H bonds has attracted great interest, because it allows the formation of C–C bonds in an atom-economic and efficient way [14–19]. In C,H insertion reactions, controlling regioselectivity against reactivity is challenging, as high reactivity often results in poor regioselectivity. An efficient C,H insertion requires the appropriate level of electrophilic character of the metallocarbenoid center. High electrophilicity of carbenoids causes poor regio- and stereocontrol, while lack of electrophilicity means lack of reactivity to insert into the unactivated C–H bond. The electronic nature of the groups that are adjacent to the C–H activation site is also important. In most cases, electron-donating groups activate the adjacent C–H bond, while electron-withdrawing groups are deactivating [20][21]. Thus, electronic, steric, and conformational factors, and catalysts affect the regioselectivity of C,H insertion reactions, and extensive efforts have been made to design molecules with suitable functional groups to give the desired products [22–25].

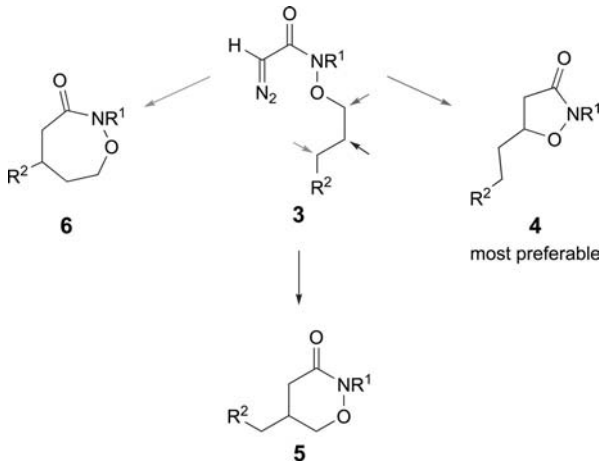
It can be stated that, in general, five-membered rings are preferable, as long as the molecule is sterically available [15]. Three-, four-, six-, and rarely higher-membered rings [26][27] can only be obtained by intramolecular C,H insertion, if the system is specially constrained [28], contains special moieties [4][5], or if the C–H bond is activated (*Scheme 2*) [27][29][30].

Starting with diazo compounds **3**, the five-membered ring **4** would be obtained *via* the entropically most favored transition state, whereas the formation of the six-membered ring **5** would also be possible. On the other hand, it has been shown that N–O-tethered diazo acetamides can insert at γ-positions to give rare seven-membered rings. It has been rationalized that electronic and/or conformational factors account for the regioselectivity observed in N–O-tethered reactions [10].

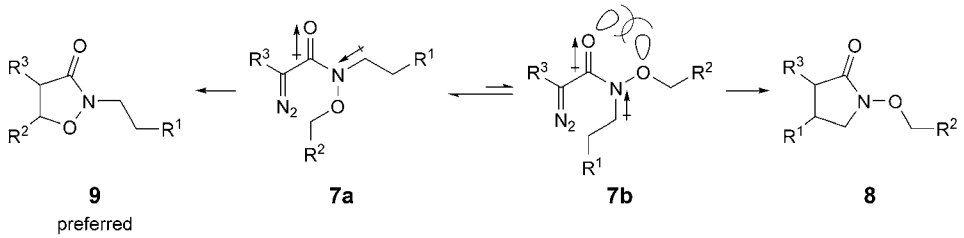
When the alkyl chains attached to the N- and O-atoms are long enough, the question arises which alkyl group will be preferred for the insertion. Conformer **7a** with alkoxy and C=O groups *s-trans* to each other is entropically more favored than conformer **7b** with *s-cis* alkoxy and C=O groups [10][31]. As shown in *Scheme 3*, lone pair–lone pair repulsion and dipol moments of conformer **7b** might result in lower stability and hinder the formation of **8**. Thus, these factors might affect C,H insertion to take place at the α-position to the O-atom in conformer **7a** to yield **9**.

Results and Discussion. – In this study, we aimed to investigate Rh^{II}-catalyzed C,H insertions on new substrates of type **3** having an N–O and ester moiety in order to obtain new heterocycles with useful functional groups which can be modified according to necessary targets. These substrates are easy to obtain with high yields *via Mitsunobu*

Scheme 2



Scheme 3



reaction under optimum conditions [6]. The *Mitsunobu* protocol is a classic reaction [32] that allows for the direct displacement of the OH group of alcohols by several nucleophiles, and several classic total syntheses of complex molecules have utilized the *Mitsunobu* protocol [33–37].

Eight different substrates, **13a**–**13h**, were prepared in high yields *via* the *Mitsunobu* protocol according to the procedure described in [6] (*Scheme 4*). The yields are given in *Table 1*.

In the Rh^{II}-catalyzed reactions of **13a**–**13d**, the C,H insertion forms five-membered rings only (*Scheme 5*). No other carbenoid product could be observed from these

Scheme 4

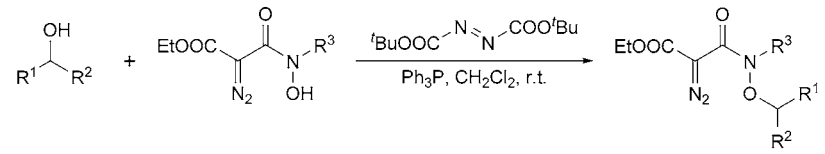
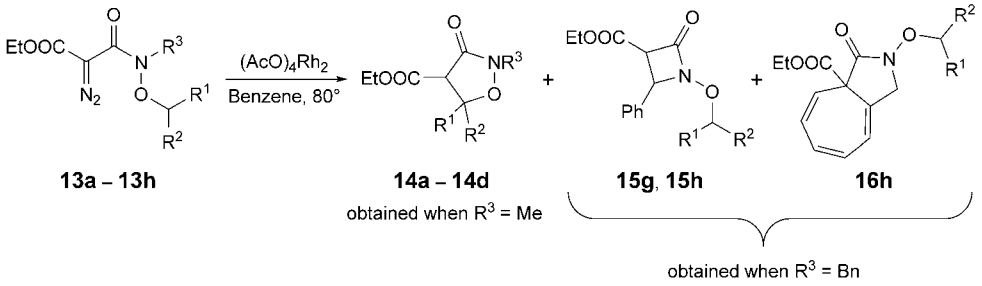


Table 1. *Yields of the* Mitsunobu *Reactions*

Entry	**10**		Diazo compound	Product	Yield [%]
	R^1	R^2			
1	MeOCH(Me)CH_2–	H	**11**	**13a**	89
2	Ph–$(CH_2)_2$–	Me	**11**	**13b**	76
3	CH_2=CH–$(CH_2)_2$–	Me	**11**	**13c**	68
4	CH_2=CH–	H	**11**	**13d**	61 [6]
5	CH≡C–$(CH_2)_2$–	H	**11**	**13e**	53
6	CH≡C–	H	**11**	**13f**	49
7	Ph–$(CH_2)_2$–	Me	**12**	**13g**	72
8	Ph–$(CH_2)_2$–	COOEt	**12**	**13h**	87

Scheme 5



reactions. This result agrees with the usual findings of several research groups [30][38–41], because five-membered ring formation is more favorable compared to other ring sizes. Also, electron-donating groups such as alkoxy substituents or O- and N-atoms facilitate the insertions on the adjacent C–H bond. The formation of the five-membered rings **14a**–**14d** took place *via* insertion at the α-position to the O-atom of the alkoxy group. No cyclopropane formation was observed in the reactions of **13c** and **13d**, which bear a tether with a C=C bond. The $(AcO)_4Rh_2$-catalyzed reaction of **13d** was tried before, but no reaction was observed at low temperature (40°) in CH_2Cl_2, although other substrates without the ester function adjacent to the diazo group yielded cyclopropane derivatives [6]. Stabilization of the carbene by the electron-withdrawing ester group lowers the reactivity of the diazo function for C,H insertions. Increasing the reaction temperature to 80° might help to activate the diazo function.

In the reactions of **13e** and **13f**, there were no starting materials left, but the products could not be isolated. GC/MS of the crude mixtures showed peaks for products with very high molecular weight. As known, sp-hybridized C-atoms are more electronegative than sp^2-hybridized C-atoms, which are in turn more electronegative than sp^3-hybridized C-atoms [42]. Due to the electrophilic nature of carbene/carbenoid, the higher reactivity of sp-hybridized C-atoms of **13e** and **13f** might result in several additions to yield compounds with high molecular weight. When a Bn group was attached to the N-atom (in **13g** and **13h**), the reactions took place at the Bn group. The β-lactam ring **15g** was solely obtained from the reaction of **13g** *via* insertion on

benzylic C–H. β-Lactam ring formation *via* benzylic C,H insertion is favorable, when a bulky group is attached to the N-atom [43]. From the reaction of **13h**, the main product was again a β-lactam ring, **15h**. Besides, product **16h** formed *via* cycloaddition to the benzene ring of the Bn group was also observed in a minor amount. Aromatic cycloaddition generally requires the deformation of the aromatic ring and if the final product will be a five-membered ring, the reaction might be prefered [44–46]. Aromatic cycloaddition was observed only in the reaction of **13h**, but not **13g**. This result may be explained because of the electron-withdrawing effect of the ester group (R^2 in **13h**), which reduces the chance of insertion on the related CH group to form the β-lactam ring.

The yields of the Rh^{II}-catalyzed reactions are given in *Table 2*.

Table 2. *Yields of Rh^{II}-Catalyzed Reactions of* **13a**–**13h**

Entry	**13**	R^1	R^2	R^3	**14** [%]	**15** [%]	**16** [%]
1	**a**	$MeOCH(Me)CH_2$–	H	Me	75[a])	–	–
2	**b**	Ph–$(CH_2)_2$–	Me	Me	51	–	–
3	**c**	CH_2=CH–$(CH_2)_2$–	Me	Me	63	–	–
4	**d**	CH_2=CH–	H	Me	71	–	–
5	**e**	CH≡C–CH_2–	H	Me	[b])	[b])	[b])
6	**f**	CH≡C–	H	Me	[b])	[b])	[b])
7	**g**	Ph–$(CH_2)_2$–	Me	Bn	–	64[a])	–
8	**h**	Ph–$(CH_2)_2$–	COOEt	Bn	–	51	11

[a]) Total yields of two isomers are given. [b]) Products with very high molecular weight.

Conclusions. – In conclusion, we have demonstrated an atom-economical way to synthesize complex heterocycles containing N–O and ester moieties. It may allow to apply known ester modifications, such as hydrolysis, substitution, and reduction [47–49], and easy N–O cleavage to synthesize targeted useful molecules [10][31]. Although a carbenoid with insufficient electrophilicity caused by an ester function lowers the reactivity for the C,H insertion [16][50–58], it was observed that this was not the only parameter. Besides carbenoid electrophilicity, the nature of the metallocarbenoid, temperature, and the substituents adjacent to the CH group, where the activation reaction takes place, affect the reaction mechanism as well. Also, the effect of an alkene function was investigated during this study, but attaching an alkene moiety to the molecule did not alter the reaction mechanism. No possible cyclopropanation was observed, and C–H activation took place under the effect of adjacent electronegative atoms. Only an aromatic ring attached to a C,H insertion center could alter the product types. With a Bn group linked to the N-atom, reactions took place *via* the N-substituted branch to yield four-membered lactams, and cycloaddition on the aromatic ring was also observed in minor amounts.

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Experimental Part

General. All reagents were obtained commercially, unless otherwise noted. Reactions were performed using oven-dried glassware under Ar atmosphere. Air- and moisture-sensitive liquids and solns. were transferred *via* syringe or stainless steel cannula. Anh. CH_2Cl_2 was distilled over CaH_2 prior to use, benzene was dried (Na wire). Thin layer chromatography (TLC): *Merck Kieselgel 60 F_{254}* plates (SiO_2); visualized by UV light. Flash column chromatography (FC): silica gel (SiO_2; 230–400 mesh). Compounds purified by FC were typically applied to the absorbent bed using the indicated solvents with a minimum amount of added CH_2Cl_2 as needed for solubility. Solvents were removed from the mixture or combined org. extracts by concentration under reduced pressure using an evaporator with bath at 35–55°. Elevated temps. were obtained using thermostat-controlled silicone oil baths. Low temps. were obtained by ice bath. IR Spectra: *PerkinElmer Spectrum One* instrument; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker AV-400* (400 and 100 MHz, resp.) or *Agilent VNMRS 500* (500 and 125 MHz, resp.); δ in ppm rel. to residual solvent peaks or indicated external standards for ^{1}H-NMR and rel. to residual solvent peak for ^{13}C-NMR, J in Hz. HR-ESI-MS: *Bruker Customer micrOTOF-Q 125* high-resolution mass spectrometer; in m/z.

Synthesis of Ethyl 2-Diazomalonyl Chloride [56]. To a dried two-necked flask equipped with thermometer were added 8.4 g (28.3 mmol) of triphosgene and 50 ml of anh. benzene. The soln. was cooled to 0°, 0.25 ml (3 mmol) of anh. pyridine were added, and a white precipitate was observed. To this mixture, 8.05 g (70 mmol, 8.5 ml from 15% CH_2Cl_2-containing soln.) of $N_2CHCOOEt$ were added dropwise. The internal temp. was kept below 10°. Then, the mixture was warmed to r.t. and stirred for 6 h under N_2 atmosphere. The red soln. was filtered and concentrated under reduced pressure. Afterwards, cold pentane was added in order to precipitate unreacted triphosgene. The mixture was filtered again and concentrated. The residue was subjected to vacuum distillation which provided 4.9 g of ethyl 2-diazomalonyl chloride as light yellow liquid in 39% yield. IR (neat): 2120, 1750, 1690. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.30 (q, J = 5.0, 2 H); 1.29 (t, J = 5.0, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 167.4; 158.6; 64.2; 62.8; 14.3.

Synthesis of Diazo Hydroxyamides **11** *and* **12**. To an oven-dried round-bottom flask were added 6 mmol of *N*-hydroxymethanamine hydrochloride (for **11**) or *N*-hydroxy-1-phenylmethanamine hydrochloride (for **12**) and 35 ml of anh. CH_2Cl_2. The soln. was cooled to 0° and 1.7 ml (12 mmol) of anh. Et_3N were added. After stirring for 10 min at 0°, 1.06 g (6 mmol) of ethyl 2-diazomalonyl chloride soln. in 25 ml anh. CH_2Cl_2 were added dropwise. The mixture was then warmed to r.t. After stirring for 1 h under N_2 atmosphere, the mixture was washed with 1% HCl and brine. The org. layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was subjected to FC to give the desired products.

Ethyl 2-Diazo-3-[hydroxy(methyl)amino]-3-oxopropanoate (**11**) [6]. Yield: 0.61 g (54%). Yellow oil.

Ethyl 3-[Benzyl(hydroxy)amino]-2-diazo-3-oxopropanoate (**12**). Yield: 1.25 g (79%). Dark yellow oil. IR (neat): 3150, 2982, 2127, 1712, 1601, 1292. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.85 (*s*, 1 H); 7.38–7.27 (*m*, 5 H); 4.82 (*s*, 2 H); 4.30 (q, J = 7.1, 2 H); 1.32 (t, J = 7.1, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 164.7; 161.7; 135.8; 128.7 (2 C); 128.5 (2 C); 127.8; 69.2; 62.6; 52.7; 14.4. HR-ESI-MS: 264.0990 ($[M+H]^+$, $C_{12}H_{14}N_3O_4^+$; calc. 264.0979).

General Procedure for the Mitsunobu *Reactions.* To a soln. of 1.0 mmol of **11** or **12** in 15 ml of anh. CH_2Cl_2 were added 144 mg (1.1 mmol) of Ph_3P in 5 ml of CH_2Cl_2 and 1.1 mmol of the corresponding alcohol **10**. Then, 253 mg (1.1 mmol) of di-*tert*-butyl azodicarboxylate soln. in 10 ml CH_2Cl_2 were added within 1 h. After stirring for 24 h at r.t., the solvent was removed under reduced pressure, and the crude mixture was subjected to FC to give the products.

Ethyl 2-Diazo-3-[(3-methoxybutoxy)(methyl)amino]-3-oxopropanoate (**13a**). Yield: 235 mg (86%). Yellow oil. IR (neat): 2973, 2120, 1729, 1650, 1372. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.29 (q, J = 7.1, 2 H); 4.03–3.91 (*m*, 2 H); 3.46–3.38 (*m*, 1 H); 3.31 (*s*, 3 H); 3.24 (*s*, 3 H); 1.78–1.72 (*m*, 2 H); 1.23 (t, J = 7.1, 3 H); 1.15 (d, J = 6.1, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 162.6; 160.8; 73.3; 70.9; 62.3; 61.6; 56.0; 34.7; 34.2; 19.0; 14.3. HR-ESI-MS: 274.1419 ($[M+H]^+$, $C_{11}H_{20}N_3O_5^+$; calc. 274.1397).

Ethyl 2-Diazo-3-{methyl[(4-phenylbutan-2-yl)oxy]amino}-3-oxopropanoate (**13b**). Yield: 242 mg (76%). Dark yellow oil. IR (neat): 2979, 2123, 1692, 1641, 1286. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.30 (t, J =

7.3, 2 H); 7.22 – 7.17 (*m*, 3 H); 4.29 (*q*, *J* = 7.1, 2 H); 4.09 – 4.01 (*m*, 1 H); 3.23 (*s*, 3 H); 2.74 – 2.68 (*m*, 2 H); 2.04 – 1.95 (*m*, 1 H); 1.85 – 1.76 (*m*, 1 H); 1.31 (*t*, *J* = 7.1, 3 H); 1.28 (*d*, *J* = 6.3, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 162.8; 160.9; 141.0; 128.5 (2 C); 128.3 (2 C); 126.1; 61.8; 35.9; 31.5; 28.1; 18.0; 14.3. HR-ESI-MS: 320.1618 ($[M+H]^+$, $C_{16}H_{22}N_3O_4^+$; calc. 320.1605).

Ethyl 2-Diazo-3-[(hex-5-en-2-yloxy)(methyl)amino]-3-oxopropanoate (**13c**). Yield: 198 mg (73%). Yellow oil. IR (neat): 2978, 2120, 1727, 1642, 1367, 1284. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.82 – 5.74 (*m*, 1 H); 5.07 – 4.98 (*m*, 2 H); 4.30 (*q*, *J* = 7.1, 2 H); 4.09 – 4.02 (*m*, 1 H); 3.25 (*s*, 3 H); 2.16 – 2.12 (*m*, 2 H); 1.80 – 1.73 (*m*, 1 H); 1.59 – 1.52 (*m*, 1 H); 1.31 (*t*, *J* = 7.1, 3 H); 1.25 (*d*, *J* = 6.2, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 162.7; 161.0; 137.3; 115.3; 79.0; 63.3; 61.5; 35.8; 33.4; 29.4; 17.9; 14.3. HR-ESI-MS: 270.1427 ($[M+H]^+$, $C_{12}H_{20}N_3O_4^+$; calc. 270.1448).

Ethyl 2-Diazo-3-[methyl(prop-2-en-1-yloxy)amino]-3-oxopropanoate (**13d**) [6]. Yield: 120 mg (53%). Yellow oil.

Ethyl 3-[(But-3-yn-1-yloxy)(methyl)amino]-2-diazo-3-oxopropanoate (**13e**). Yield: 86 mg (38%). Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.31 (*q*, *J* = 7.1, 2 H); 4.03 (*t*, *J* = 6.6, 2 H); 3.29 (*s*, 3 H); 2.55 (*td*, *J* = 6.6, 2.6, 2 H); 2.05 (*t*, *J* = 2.6, 1 H); 1.33 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 162.3; 161.4; 79.5; 71.8; 70.1; 61.6; 34.9; 18.1; 14.3. HR-ESI-MS: 240.0974 ($[M+H]^+$, $C_{10}H_{14}N_3O_4^+$; calc. 240.0979).

Ethyl 2-Diazo-3-[methyl(prop-2-yn-1-yloxy)amino]-3-oxopropanoate (**13f**). Yield: 118 mg (49%). Yellow oil. IR (neat): 2982, 2121, 1723, 1641, 1369. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.54 (*d*, *J* = 2.4, 2 H); 4.30 (*q*, *J* = 7.1, 2 H), 3.31 (*s*, 3 H); 2.61 (*t*, *J* = 2.4, 1 H); 1.32 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 162.3; 161.8; 77.5; 76.5; 61.8; 61.6; 35.3; 14.3. HR-ESI-MS: 226.0835 ($[M+H]^+$, $C_9H_{12}N_3O_4^+$; calc. 226.0822).

Ethyl 3-{Benzyl[(4-phenylbutan-2-yl)oxy]amino}-2-diazo-3-oxopropanoate (**13g**). Yield: 284 mg (72%). Yellow oil. IR (neat): 2977, 2932, 2122, 1657, 1642, 1367. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 – 7.27 (*m*, 7 H); 7.22 (*d*, *J* = 7.4, 1 H); 7.11 (*d*, *J* = 6.9, 2 H); 4.89 (*d*, *J* = 15.5, 1 H); 4.72 (*d*, *J* = 15.5, 1 H); 4.32 (*qd*, *J* = 7.1, 1.7, 2 H); 4.02 – 3.94 (*m*, 1 H); 2.61 – 2.56 (*m*, 2 H); 2.00 – 1.91 (*m*, 1 H); 1.82 – 1.71 (*m*, 1 H); 1.33 (*t*, *J* = 7.1, 3 H); 1.25 (*d*, *J* = 6.2, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 161.5; 155.7; 141.0; 136.1; 128.5 (2 C); 128.4 (2 C); 128.3 (2 C); 128.2 (2 C); 127.7; 126.0; 79.3; 61.6; 51.9; 35.8; 28.1; 17.9; 14.3. HR-ESI-MS: 396.1941 ($[M+H]^+$, $C_{22}H_{26}N_3O_4^+$; calc. 396.1918).

Ethyl 2-{[Benzyl(2-diazo-3-ethoxy-3-oxopropanoyl)amino]oxy}-4-phenylbutanoate (**13h**). Yield: 394 mg (87%). Yellow oil. IR (neat): 2980, 2928, 2129, 1650, 1370. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.38 – 7.23 (*m*, 8 H); 7.12 (*d*, *J* = 7.2, 2 H); 4.93 (*d*, *J* = 15.8, 1 H); 4.77 (*d*, *J* = 15.8, 1 H); 4.39 (*t*, *J* = 6.5, 1 H); 4.33 (*q*, *J* = 7.1, 2 H); 4.17 (*q*, *J* = 7.2, 2 H); 2.70 – 2.57 (*m*, 2 H); 2.08 – 2.01 (*m*, 2 H); 1.33 (*t*, *J* = 7.1, 3 H); 1.27 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 176.6; 170.0; 162.4; 140.0; 135.9; 128.6 (2 C); 128.5 (2 C); 128.3 (2 C); 128.2 (2 C); 127.8; 126.3; 81.6; 61.6; 61.5; 52.8; 32.3; 31.0; 14.3; 14.0. HR-ESI-MS: 454.1971 ($[M+H]^+$, $C_{24}H_{28}N_3O_6^+$; calc. 454.1973).

General Procedure for C–H Activation Reactions. Diazo compounds **13a** – **13h** (0.50 mmol), throughly dried to minimize H_2O content, were dissolved in benzene (10 ml) and degassed for 20 min. $(AcO)_4Rh_2$ (4.6 mg) and 25 ml of benzene were added to a dried three-necked flask equipped with condenser and degassed for 20 min. Then, the soln. of the diazo compound was added *via* a syringe pump over 1 h. The mixture was stirred under reflux (80°) for 4 h. The solvent was then evaporated and the product was purified by FC (hexane/AcOEt).

Ethyl 5-(2-Methoxypropyl)-2-methyl-3-oxo-1,2-oxazolidine-4-carboxylate (**14a**). Yield: 97 mg (75%, mixture (ratio 1 : 1.8) of two isomers, **14a_i** and **14a_ii**). ^{1}H-NMR (400 MHz, $CDCl_3$) for **14a_i**: 4.95 – 4.91 (*m*, 1 H); 4.35 – 4.24 (*m*, 2 H); 3.58 (*d*, *J* = 10.1, 1 H); 3.37 – 3.32 (*m*, 1 H); 3.25 (*s*, 3 H); 3.19 (*s*, 3 H); 1.87 – 1.80 (*m*, 4 H); 1.35 (*t*, *J* = 7.1, 3 H); 1.19 (*d*, *J* = 6.1, 3 H). ^{1}H-NMR (400 MHz, $CDCl_3$) for **14a_ii:** 4.97 – 4.92 (*m*, 1 H); 4.35 – 4.24 (*m*, 2 H); 3.63 (*d*, *J* = 10.0, 1 H); 3.37 – 3.32 (*m*, 1 H); 3.28 (*s*, 3 H); 3.20 (*s*, 3 H); 2.05 – 1.99 (*m*, 4 H); 1.34 (*t*, *J* = 7.1, 3 H); 1.22 (*d*, *J* = 6.2, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$) for **14a_i**: 167.2; 164.9; 78.9; 73.1; 61.9; 56.2; 55.7; 39.0; 31.8 (2 C); 19.0; 14.1. ^{13}C-NMR (125 MHz, $CDCl_3$) for **14a_ii**: 167.2; 164.9; 78.2; 72.9; 62.0; 56.2; 55.8; 39.0; 31.8 (2 C); 18.7; 14.1. HR-ESI-MS: 246.1352 ($[M+H]^+$, $C_{11}H_{20}NO_5^+$; calc. 246.1336).

Ethyl 2,5-Dimethyl-3-oxo-5-(2-phenylethyl)-1,2-oxazolidine-4-carboxylate (**14b**). Yield: 74 mg (51%). IR (neat): 3021, 2928, 1742, 1682, 1370. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.40 – 7.28 (*m*, 3 H);

7.25–7.19 (*m*, 2 H); 4.22 (*q*, *J* = 7.1, 2 H); 3.37 (*s*, 1 H); 3.22 (*s*, 3 H); 2.47 (*t*, *J* = 7.3, 2 H); 1.61–1.55 (*m*, 2 H); 1.32 (*t*, *J* = 7.0, 3 H); 1.28 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 168.1; 166.1; 139.9; 128.5 (2 C); 128.2; 127.9; 126.3; 72.9; 64.5; 61.2; 39.7; 33.2; 30.6; 25.1; 14.2. HR-ESI-MS: 292.1554 ($[M+H]^+$, $C_{16}H_{22}NO_4^+$; calc. 292.1543).

Ethyl 5-(But-3-en-1-yl)-2,5-dimethyl-3-oxo-1,2-oxazolidine-4-carboxylate (**14c**). Yield: 76 mg (63%). Yellow oil. IR (neat): 2981, 1725, 1632, 1364. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.89–5.77 (*m*, 1 H); 5.11–4.99 (*m*, 2 H); 4.43 (*q*, *J* = 7.1, 2 H); 3.85 (*s*, 3 H); 3.21 (*s*, 1 H); 2.25–2.16 (*m*, 2 H); 1.44 (*t*, *J* = 6.4, 2 H); 1.38 (*s*, 3 H); 1.32 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 167.4; 165.9; 134.3; 120.2; 80.3; 63.5; 62.2; 39.0; 31.9; 25.3; 21.8; 14.1. HR-ESI-MS: 242.1399 ($[M+H]^+$, $C_{12}H_{20}NO_4^+$; calc. 242.1387).

Ethyl 5-Ethenyl-2-methyl-3-oxo-1,2-oxazolidine-4-carboxylate (**14d**). Yield: 71 mg (71%). Dark yellow oil. IR (neat): 3000, 1717, 1666, 1369. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.95–5.88 (*m*, 1 H); 5.51 (*dt*, *J* = 17.2, 1.0, 1 H); 5.42 (*dt*, *J* = 10.4, 0.9, 1 H); 5.21 (*ddt*, *J* = 10.0, 6.9, 0.9, 1 H); 4.30 (*q*, *J* = 7.1, 2 H); 3.63 (*d*, *J* = 10.0, 1 H); 3.22 (*s*, 3 H); 1.34 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 167.7; 166.5; 132.1; 121.1; 81.2; 62.2; 55.2; 31.9; 14.1. HR-ESI-MS: 200.0927 ($[M+H]^+$, $C_9H_{14}NO_4^+$; calc. 200.0917).

Ethyl 2-Oxo-4-phenyl-1-[(4-phenylbutan-2-yl)oxy]azetidine-3-carboxylate (**15g**). Yield: 117 mg (64%, mixture (ratio 1:1.6) of two isomers, **15g_i** and **15g_ii**). IR (neat, for the mixture): 3064, 2980, 2935, 1752, 1730, 1442, 1316. ^{1}H-NMR (400 MHz, $CDCl_3$) for **15g_i**: 7.45–7.38 (*m*, 5 H); 7.26–7.17 (*m*, 3 H); 7.10 (*d*, *J* = 6.8, 2 H); 5.10 (*d*, *J* = 2.3, 1 H); 4.29 (*q*, *J* = 7.1, 2 H); 4.09–3.98 (*m*, 1 H); 3.70 (*d*, *J* = 2.4, 1 H); 2.68–2.57 (*m*, 2 H); 2.06–1.88 (*m*, 1 H); 1.83–1.70 (*m*, 1 H); 1.33 (*t*, *J* = 7.1, 3 H); 1.32 (*d*, *J* = 6.2, 3 H). ^{1}H-NMR (400 MHz, $CDCl_3$) for **15g_ii**: 7.45–7.38 (*m*, 5 H); 7.26–7.17 (*m*, 3 H); 7.03 (*d*, *J* = 6.8, 2 H); 5.08 (*d*, *J* = 2.1, 1 H); 4.28 (*qd*, *J* = 7.1, 0.9, 2 H); 4.09–3.98 (*m*, 1 H); 3.69 (*d*, *J* = 2.2, 1 H); 2.68–2.57 (*m*, 2 H); 2.06–1.88 (*m*, 1 H); 1.83–1.70 (*m*, 1 H); 1.33 (*t*, *J* = 7.1, 3 H); 1.32 (*d*, *J* = 6.2, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$) for **15g_i**: 169.8; 164.5; 142.8; 141.7; 128.7 (3 C); 128.5; 128.4 (3 C); 126.9 (2 C); 126.2; 78.1; 63.3; 61.0; 47.9; 37.5; 31.3; 21.2; 14.1. ^{13}C-NMR (125 MHz, $CDCl_3$) for **15g_ii**: 169.8; 164.2; 142.8; 141.9; 128.7 (3 C); 128.5; 128.4 (3 C); 126.9 (2 C); 126.1; 78.0; 63.3; 59.6; 47.3; 37.5; 31.3; 21.2; 14.1. HR-ESI-MS: 368.1877 ($[M+H]^+$, $C_{22}H_{26}NO_4^+$; calc. 368.1856).

Ethyl 1-[(1-Ethoxy-1-oxo-4-phenylbutan-2-yl)oxy]-2-oxo-4-phenylazetidine-3-carboxylate (**15h**). Yield: 108 mg (51%). Yellow oil. IR (neat): 2980, 1761, 1727, 1645, 1496, 1371. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.44–7.40 (*m*, 2 H); 7.33–7.28 (*m*, 4 H); 7.25–7.22 (*m*, 4 H); 5.38 (*d*, *J* = 4.8, 1 H); 4.30–4.16 (*m*, 4 H); 4.24 (*q*, *J* = 7.1, 2 H); 2.37 (*t*, *J* = 7.5, 2 H); 2.32–2.28 (*m*, 2 H); 1.31 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 169.9 (2 C); 165.2; 143.0; 141.7; 128.9 (2 C); 128.4 (2 C); 127.8; 127.7; 126.9 (2 C); 126.4; 125.9; 85.5; 62.1; 61.7; 60.0; 47.4; 33.4; 31.8; 14.1; 14.0. HR-ESI-MS: 426.1928 ($[M+H]^+$, $C_{24}H_{28}NO_6^+$; calc. 426.1911).

Ethyl 2-[(1-Ethoxy-1-oxo-4-phenylbutan-2-yl)oxy]-3-oxo-2,3-dihydrocyclohepta[c]pyrrole-3a(1H)-carboxylate (**16h**). Yield: 23 mg (11%). Dark yellow oil. IR (neat): 2981, 2925, 1761, 1734, 1725, 1645, 1466, 1363. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.43–7.40 (*m*, 1 H); 7.33–7.13 (*m*, 4 H); 6.51–6.44 (*m*, 2 H); 6.35–6.31 (*m*, 1 H); 5.62 (*d*, *J* = 9.5, 1 H); 5.57 (*d*, *J* = 9.3, 1 H); 4.27 (*q*, *J* = 7.0, 2 H); 4.13 (*t*, *J* = 7.0, 1 H); 4.10 (*q*, *J* = 7.1, 2 H); 3.93–3.89 (*m*, 2 H); 2.92 (*t*, *J* = 7.2, 2 H); 2.23–2.16 (*m*, 2 H); 1.32 (*t*, *J* = 7.1, 3 H); 1.28 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 169.9; 166.2; 165.8; 143.5; 143.0; 138.1; 134.7; 129.5; 128.5 (2 C); 127.6; 127.3; 126.0; 125.5; 124.9; 87.2; 62.8; 61.6; 59.5; 47.0; 32.9; 31.9; 14.2; 14.1. HR-ESI-MS: 426.1931 ($[M+H]^+$, $C_{24}H_{28}NO_6^+$; calc. 426.1911).

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