Synthetic Methods

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Development of a Povarov Reaction/Carbene Generation Sequence for Alkenyldiazocarbonyl Compounds**

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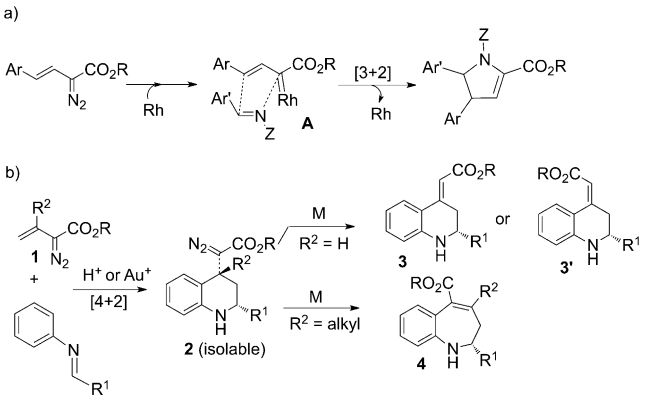
Metal-catalyzed cycloadditions of alkenyldiazo reagents are useful tools to access carbo- and heterocycles.[1] These diazo compounds are chemically sensitive toward both Brønsted or Lewis acids. Their reported cycloadditions rely heavily on the formation of metal carbenes to initiate regio- and stereoselective [3+*n*] cycloadditions ($n = 2$–4) with suitable dipolarophiles.[2–4] A noncarbene route was postulated for a few copper-catalyzed cycloadditions of these diazo species, but they resulted in complete diazo decomposition.[3a,4a,5]

Doyle and co-workers reported[4a] a [3+2] cycloaddition of the alkenylrhodium carbene **A** with imines to give dihydropyrroles (Scheme 1 a). We proposed a cycloaddition route with analogous reagents to secure their versatile diazo functionalities. Toward this objective, we developed an unprecedented cycloaddition route (Scheme 1 b) involving an initial formal [4+2] cycloaddition (Povarov[6,7] reaction) between the diazo species **1** and N-aryl imines to give isolable diazo-containing cycloadducts (**2**) stereoselectively. The subsequent formation of their metal carbenes allows efficient production of six- and seven-membered azacycles including the tetrahydroquinoline derivatives **3** and **3′**, as well as the tetrahydro-1*H*-benzo[*b*]azepine species **4**.



Scheme 1. Cycloaddition routes for alkenyldiazo species. a) Metal carbene routes (current pathways).[2–4] b) Cycloaddition route (this work).

Access to these frameworks are valuable for the preparation of several bioactive molecules including 2-phenyl-2,3-dihydroquinolone,[8a] L-689,560,[8b] torcetrapib,[8c] martinellic acid,[8d] OPC-31260,[8e] OPC-51803,[8f] and tetraperalone A (Figure 1).[8g] Their specific biological functions have been well documented.[8]

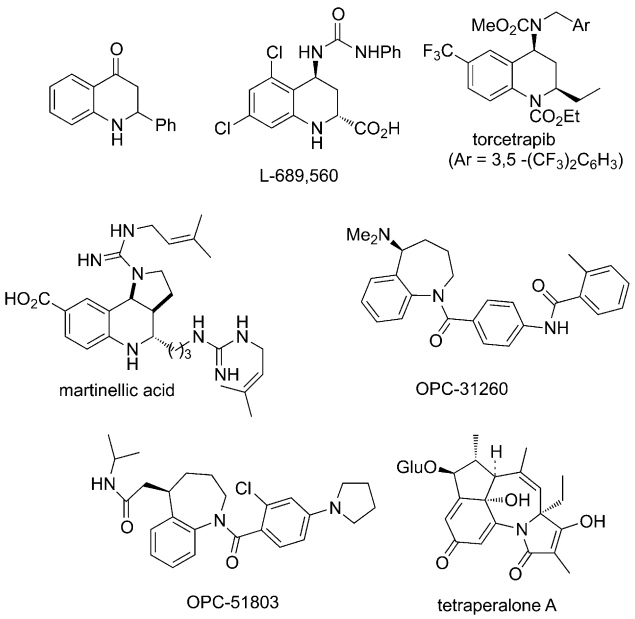


Figure 1. Accessible biologically active molecules.

Shown in Table 1 are our efforts to realize a Povarov[6,7] reaction between the *N*-benzylideneaniline [**I**(**a**)] and ethyl vinyldiazoacetate (**1a**) using various acid catalysts; the duration of reaction pertains to the complete consumption of **1a**. We selected **I**(**a**) as the target because of its great affinity toward metal coordination, possibly impeding diazo decomposition. As shown in entry 1, treatment of a 1,2-dichloroethane (DCE) solution of **1a** (1.0 equiv) and **I**(**a**) (1.1 equiv) with $[Rh_2(OAc)_4]$ (2.5 mol %) at 28 °C (4 h) gave a complex mixture of products. Under the same reaction conditions, $Cu(OTf)_2$ (5 mol %, entry 2) gave the cycloadduct **2a** (18 %) together with the *E*- and *Z*-configured unsaturated esters **3a** (48 %) and **3a′** (27 %), respectively, and they were separable on a silica gel column. We sought to improve the chemoselectivity by using various gold catalysts (entries 3–5). $[PPh_3AuCl]/AgNTf_2$ gave the unsaturated esters **3a** and **3a′** in 55 and 30 % yields, respectively (entry 3). With $[P(tBu)_2(o$-

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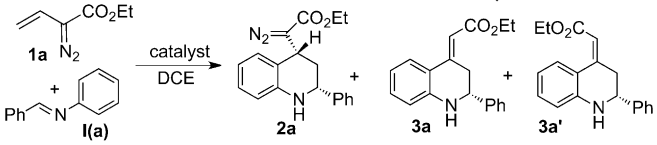
Table 1: Test of Povarov reactions on various acid catalysts.[a]

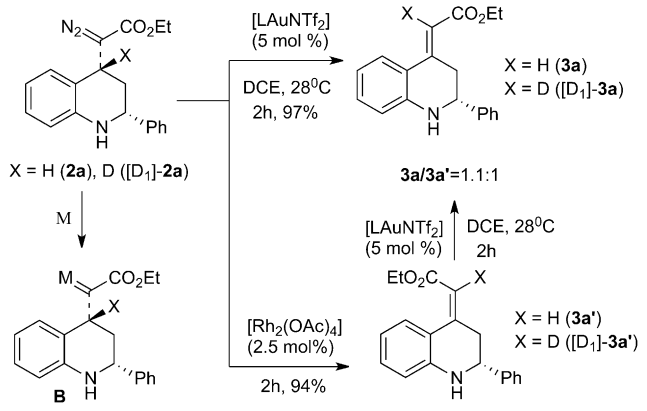


Entry	Catalyst (mol%)	T [°C]	t [h]	Yield [%][b]		
				2a	**3a**	**3a′**
1	$[Rh_2(OAc)_4]$ (2.5)	28	4	–	–	–[c]
2	$Cu(OTf)_2$ (5)	28	2	18	48	27
3	$[PPh_3AuCl]/AgNTf_2$ (5)	28	2	–	55	30
4	$[LAuCl]/AgNTf_2$ (5)	28	2	60	32	–
5	$[LAuCl]/AgNTf_2$ (5)	60	4	–	84	–
6	$[IPrAuCl]/AgNTf_2$ (5)	28	2	82	–	–
7	$AgNTf_2$ (5)	28	2	–	–	–
8	HOTf (3)	28	0.2	95	–	–

[a] **1a** (1.0 equiv), **I(a)** (1.1 equiv), [**1a**] = 0.57 M. [b] Product yields are given for products isolated after purification using a silica gel column. [c] Complicated mixture of products. L = P(tBu)$_2$(o-biphenyl), Tf = trifluoromethanesulfonyl.

biphenyl)AuNTf$_2$] (entry 4), we obtained the desired **2a** as the major product (60%) in addition to **3a** (32%). With this gold catalyst in hot DCE (60°C, 4 h), we obtained **3a** in 84% yield. To our pleasure, the use of the less acidic [IPrAuNTf$_2$] (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) allowed efficient production of **2a** exclusively (entry 6). In a control experiment, AgNTf$_2$ alone gave a complex mixture of products in DCE (28°C). Particularly appealing is HOTf (3 mol%), which gave **2a** stereoselectively (d.r. > 20:1) with a yield of up to 95% after a short reaction time (entry 8).[7] We postulate that the tetrahydroquinoline framework in **2a** is slightly basic and protects the diazo group from HOTf decomposition. The stereochemistry of **2a** is supported by the ^{1}H NOE data. The structure of **3a** was confirmed by X-ray diffraction.[9]

The diazo-containing cycloadduct **2a** is can be used in the stereoselective syntheses of **3a** and **3a′** via the carbene intermediate **B** (Scheme 2). The treatment of **2a** with [P(tBu)$_2$(o-biphenyl)AuNTf$_2$] in DCE (28°C, 2 h) gave **3a** in 97% yield, whereas [Rh$_2$(OAc)$_4$] (2.5 mol%) gave only **3a′** in 94% yield under the same reaction conditions. With deuterated [D$_1$]-**2a** (X = D), the same Au and Rh catalysts delivered

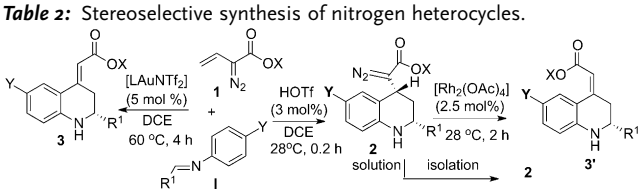


Scheme 2. Transformations into metal carbenes.

the E-configured ester [D$_1$]-**3a** and Z-configured ester [D$_1$]-**3a′**, respectively, with full deuterium content at their olefin positions. The treatment of **3a′** with [P(tBu)$_2$(o-biphenyl)-AuNTf$_2$] in DCE (28°C, 2 h) gave mixture of **3a** and **3a′** (1.1:1). We postulate that the 1,2-hydride shift proceeds stereoselectively for the Au and Rh carbenes **B**; the former favors E-alkene selectivity[10] whereas the latter produces Z alkenes preferably.[11]

We tested the reactions of the diazo reagents **1a–c** with various imines [**I(a)**–**(i)**] to generalize the stereoselective synthesis of the cycloadducts **2**, together with the E- and Z-esters **3** and **3′** (Table 2). We obtained the cycloadducts **2** and E-configured esters **3** directly from the starting reagents using

Table 2: Stereoselective synthesis of nitrogen heterocycles.



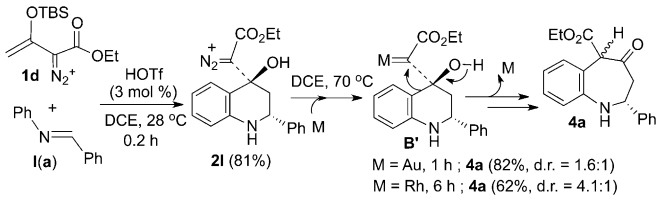
Entry	**1**[a] (X)	**I**[b] (Y, R^1)	Yield [%]		
			2[c]	**3**[d]	**3′**[e]
1	**1a** (Et)	**I(b)** (OMe, Ph)	**2b**: 83	**3b**: 77	**3b′**: 68
2	**1a**	**I(c)** (CF_3, Ph)	**2c**: 89	**3c**: 79	**3c′**: 72
3	**1a**	**I(d)** (Cl, Ph)	**2d**: 84	**3d**: 82	**3d′**: 67
4	**1a**	**I(e)** (H, 4-MeOC$_6$H$_4$)	**2e**: 84	**3e**: 74	**3e′**: 73
5	**1a**	**I(f)** (H, 4-ClC$_6$H$_4$)	**2f**: 89	**3f**: 75	**3f′**: 72
6	**1a**	**I(g)** (H, 2-furanyl)	**2g**: 86	**3g**: 76	**3g′**: 70
7	**1a**	**I(h)** (H, *n*Pr)	**2h**: 81	**3h**: 72	**3h′**: 60
8	**1a**	**I(i)** (H, CO_2Et)	**2i**: 84	**3i**: 74	**3i′**: 67
9	**1b** (tBu)	**I(a)** (H, Ph)	**2j**: 89	**3j**: 86	**3j′**: 73
10	**1c** (Bn)	**I(a)**	**2k**: 84	**3k**: 85	**3k′**: 74

[a] **1** (1.0 equiv). [b] Imine (1.1 equiv), [substrate] = 0.57 M. [c] For reaction using HOTf. Yields are given for product isolated after purification using a silica gel column. [d] For reaction using [LAuNTf$_2$]. Yields are given for product isolated after purification using a silica gel column. [e] For reaction using H$^+$/Rh. Yields are given for product isolated after purification using a silica gel column. L = P(tBu)$_2$(o-biphenyl).

HOTf (3 mol%) and [P(tBu)$_2$(o-biphenyl)AuNTf$_2$] (5 mol%) respectively, under the optimum reaction conditions detailed in entries 5 and 8 of Table 1. Production of the Z-configured esters **3′** relies on an initial treatment of the reagents with HOTf (3 mol%), and subsequent addition of [Rh$_2$(OAc)$_4$] (2.5 mol%) to the same DCE solution. The three reactions worked well for the imines **I(b)**–**(d)** bearing *para*-methoxy, *para*-trifluoromethyl, and *para*-chloro substituents, respectively, on their aniline moieties. The resulting products **2b–d**, **3b–d**, and **3b′–d′** were obtained with satisfactory yields (entries 1–3). For **I(e)**,**(f)** bearing 4-MeOC$_6$H$_4$ and 4-ClC$_6$H$_4$, respectively, the corresponding products **2e**,**f, 3e**,**f**, and **3e′**,**f′** were obtained with yields greater than 72% (entries 4 and 5). These catalytic reactions can be used for the imines **I(g)**–**(i)** bearing 2-furanyl, *n*-propyl, and ester groups, respectively, thus giving the desired compounds **2g–i**, **3g–i**, and **3g′–i′** in reasonable yields (entries 6–8). We tested the reactions on the α-diazo esters **1b**,**c**, thus producing the expected cycloadducts **2j**,**k** by using HOTf as the catalyst. We obtained the E- (**3j**,**k**)

and *Z*-configured (**3j′**,**k′**) esters using the Au and Rh catalysts, respectively (entries 9 and 10).

To expand the scope of the diazo substrates, we examined the HOTf-catalyzed cycloaddition of the β-substituted diazoester **1d** with **I(a)** in DCE (28 °C, 0.2 h), thus giving the desired cycloadduct **2l** (d.r. > 20:1) in 81 % yield (Scheme 3).

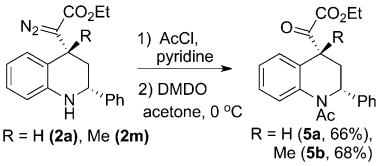


Scheme 3. Reactions of the 2-substituted alkenyldiazo species **1d**. TBS = *tert*-butyldimethylsilyl.

Interestingly, the treatment of the cycloadduct **2l** with $[P(t\mathrm{Bu})_2(o\text{-biphenyl})\mathrm{AuNTf_2}]$ in hot DCE (70 °C, 1 h) gave the seven-membered azacycle **4a** in 82 % yield, albeit with low diastereoselectivity (d.r. = 1.6:1). $[Rh_2(OAc)_4]$ gave the same azacycle with a better d.r. value (4.1:1), but a decreased yield (62 %).

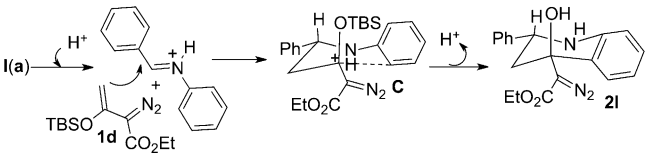
These Povarov reactions are amenable to the β-substituted diazoesters **1e–j** using HOTf as a catalyst (3 mol %), and the resulting cycloadducts **2m–s** were produced with a diastereoselectivity of greater than 4:1 (Table 3). We also obtained the seven-membered azacycles **4b–h** in a one-pot operation involving treatment of the cycloadducts **2** in situ with $[P(t\mathrm{Bu})_2(o\text{-biphenyl})\mathrm{AuNTf_2}]$ (5 mol %) in DCE (28 °C, 1 h). For the methyl-substituted diazo species **1e**, cycloaddition with **I(a)** and **I(l)** gave the corresponding cycloadducts **2m** and **2n** stereoselectively (d.r. > 20:1), and the seven-membered azacycles **4b** and **4c** were obtained in 67–76 % yields (entries 1 and 2). The stereochemistry of **2m** was determined by X-ray diffraction.[9] Excellent diastereoselectivity was also obtained for the cycloadducts **2o** and **2p**, which were derived from the diazo substrates **1f** and **1g**, respectively (entries 3 and 4). The seven-membered azacycles **4d** and **4e** were also produced in good yields (75–76 %). For the remaining diazoesters **1h–j** (entries 5–7), we obtained two diastereomeric products (d.r. = 4:1–4.4:1) for compounds **2q** (R^2 = *n*-butyl), **2r**, and **2s** which were separable on a silica gel column. Gold carbene generation in situ for these isomeric mixtures gave the seven-membered azacycles **4f–h** in 67–82 % yields. The molecular structure of **4f** was confirmed by X-ray diffraction.[9]

Equation (1) highlights the functionalization of the diazo group of **2a** and **2m**. Dimethyldioxirane (DMDO)[12] oxidation of the acetyl derivatives of these two azacycles in cold THF (0 °C) gave the α-keto esters **5a** and **5b** in 66 and 68 %, yields respectively.



(1)

Scheme 4 depicts a plausible path to rationalize the stereochemical course of the resulting cycloadducts, a path involving the initial reaction of HOTf with **1d**.[7] According to

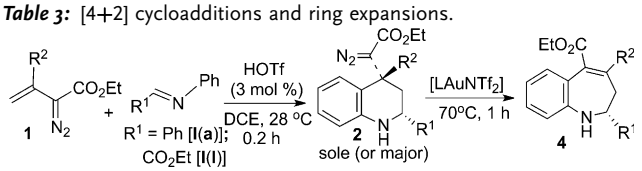


Scheme 4. A plausible model for stereochemistry.

a preferable stepwise mechanism,[6b] the formation of an initial C–C bond generates the chairlike transition-state **C** which has the small hydrogen and OTBS substituents in axial positions, thus generating the cycloadduct **2l** with the observed stereochemistry. For other less polarized alkenyldiazo species, including **1a–c** and **1e–j**, the cycloadditions likely proceed in a concerted endo fashion.[6c–e]

Inspired by our success in the preceding Povarov reactions catalyzed with triflic acid, we investigated accessing diazo-containing oxacycles by an unprecedented oxa-Povarov reaction via the postulated benzylidene(phenyl)oxonium **D** (Table 4). Treatment of an equimolar mixture of ethyl vinyldiazoacetate (**1a**; 0.57 M) and (diphenoxymethyl)benzene (**6a**) with HOTf (3 mol %) in cold DCE (−30 °C, 10 min) led to the rapid decomposition of **6a** into phenol and benzaldehyde. After some optimization, we found that the presence of α-phenylethylamine (2 mol %) in this triflic acid system delivered the desired diazo-containing oxacycle **7a** as a single diastereomer in 75 % yield (entry 1). The role of this primary amine is to decrease the acidity of the reaction medium. The stereochemistry of **7a** was confirmed by ^{1}H NOE and NMR data. This oxa-Povarov reaction worked well for the acetals **6b–e** to give the desired oxacycles **7b–**

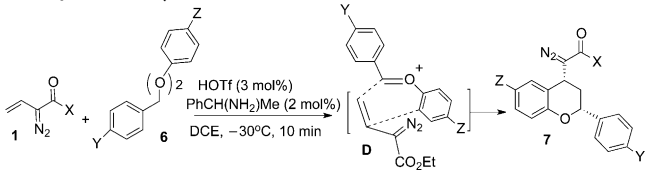
Table 3: [4+2] cycloadditions and ring expansions.



Entry	**1**[a] (R^2)	I[b]	Yield [%] **2**[c]	**4**[d]
1	**1e** (Me)	I(a)	**2m**: 82 (d.r. > 20:1)	**4b**: 76
2	**1e**	I(l)	**2n**: 72 (d.r. > 20:1)	**4c**: 67
3	**1f** (Cy)	I(a)	**2o**: 80 (d.r. > 20:1)	**4d**: 75
4	**1g** (Bn)	I(a)	**2p**: 83 (d.r. > 20:1)	**4e**: 76
5	**1h** (*n*Bu)	I(a)	**2q**: 86 (d.r. = 4:1)	**4f**: 73
6	**1i** (3-methylbutyl)	I(a)	**2r**: 88 (d.r. = 4.4:1)	**4g**: 67
7	**1j** (3-methyl-3-butenyl)	I(a)	**2s**: 88 (d.r. = 4.4:1)	**4h**: 82

[a] **1** (1.0 equiv). [b] Imine (1.1 equiv), [substrate] = 0.57 M. [c] For reaction using HOTf. Yields are given for product isolated after purification using a silica gel column. [d] For reaction using H^+/Au. Yields are given for product isolated after purification using a silica gel column.

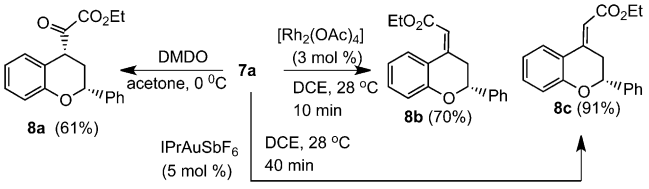
Table 4: Feasibility of an oxa-Povarov reaction.



Entry	**1**[a] (X)	**6**[b] (Y, Z)	**7**: Yield [%][c]
1	**1a** (OEt)	**6a** (H, H)	**7a**: 75
2	**1a**	**6b** (H, OMe)	**7b**: 77
3	**1a**	**6c** (H, Cl)	**7c**: 72
4	**1a**	**6d** (Me, H)	**7d**: 69
5	**1a**	**6e** (Cl, H)	**7e**: 56
6	**1b** (O*t*Bu)	**6a**	**7f**: 74
7	**1k** (Ph)	**6a**	**7g**: 76
8	**1l** (*n*Pr)	**6a**	**7h**: 68

[a] **1a** (0.57 M). [b] Acetal (1.1 equiv). [c] Yields are given for product isolated after purification using a silica gel column.

e stereoselectively (entries 2–5). The generality of this unprecedented cycloaddition is again manifested with its applicability to various alkenyldiazo compounds (**1b**,**k** and **l**), thus giving the cycloadducts **7f–h** in 68–76% yields (entries 6–8). Using our methods discussed above, the compound **7a** was converted into the dicarbonyl species **8a**, and the *Z*- and *E*-configured esters **8b** and **8c**, respectively, with 61–91% yields (Scheme 5).



Scheme 5. Chemical functionalization of diazo compound **7a**.

Reported catalytic cycloadditions on alkenyldiazo reagents are inevitably accompanied by a diazo decomposition. We have developed a HOTf-catalyzed Povarov reaction for these diazo species to give diazo-containing cycloadducts stereoselectively. The resulting cycloadducts provide access to various six- and seven-membered azacycles, by either the generation of metal carbenes or the functionalization of the diazo group. Our preliminary results also reveal the feasibility of oxa-Povarov reactions, which are unknown in the literature. Future work will be focused on the asymmetric versions of these new reactions.

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