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Tetrahydroquinolines and Benzazepines through Catalytic Diastereoselective Formal [4 + 2]-Cycloaddition Reactions between Donor–Acceptor Cyclopropenes and Imines

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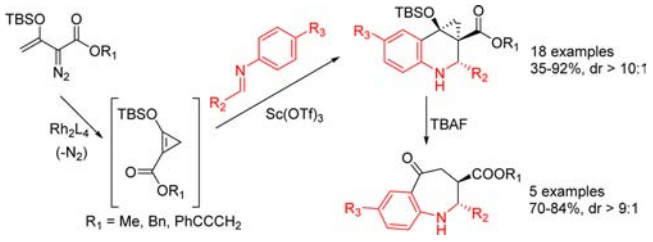
ABSTRACT



Regio- and diastereoselective Lewis acid catalyzed cycloaddition reactions between imines and donor–acceptor cyclopropenes generated from silyl-protected enoldiazoacetates provide direct access to stable cyclopropane-fused tetrahydroquinolines and, with cyclopropane ring opening under mild conditions, to 1*H*-benzazipine derivatives.

Access to heterocyclic nitrogen-containing compounds is of ongoing interest to synthetic and medicinal chemists because of their abundance in natural products and their biological activities.[1] Among these heterocycles, tetrahydroquinolines and benzazepines represent two important classes that form the structural motif of many medicinally relevant compounds.[2] As examples, the cyclopropane-fused hydroquinoline **1** is an HIV-1 non-nucleoside reverse transcriptase inhibitor with potency on the nanomolar scale.[3a] Benzazepine tolvaptan (**2**) is an approved drug for treatment of hyponatremia,[3b] and benazepril (**3**) is an angiotensin-converting enzyme inhibitor used to treat hypertension (Scheme 1).[3c] The preparation of these structural scaffolds requires multistep syntheses,[2,3] and this requirement invites more efficient methodologies for the construction of these functionalized structural units.[4]

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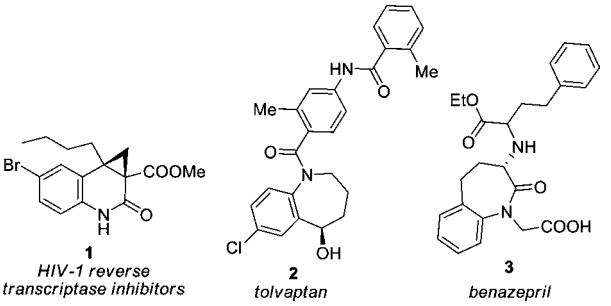
Scheme 1. Examples of Biologically Active Tetrahydroquinoline and Benzazepine Heterocycles



Metal catalyzed dinitrogen extrusion from diazo compounds through metal carbene intermediates is a versatile route to access carbocyclic and heterocyclic ring systems.[5] Our group has recently focused on the metal catalyzed reactions of silyl-protected enoldiazoacetates **4** (Scheme 2) that generate metal enol carbene intermediates (**5**) which are known to undergo cycloaddition,[6a,b] N−H insertion,[6c,d] and nucleophilic addition reactions.[6e] However, as Davies and co-workers have shown,[7] if capture of **5** is slow, rearrangement occurs to form donor−acceptor cyclopropenes **6** that, for example, have been trapped with cyclopentadiene to form bicyclo[3.2.1]octadiene **7**. Although, these interesting donor−acceptor cyclopropenes were discovered almost two decades ago, their synthetic potential has not yet been fully explored. We recently discovered that cyclopropenes **6** undergo dipolar cycloaddition with nitrile oxides followed by rearrangement to form furanones **8** (Scheme 2),[8] and we now wish to report a Povarov-type reaction[9] between

Scheme 2. Catalytic Dinitrogen Extrusion from Enoldiazoacetate **4** and Its Subsequent Reactions

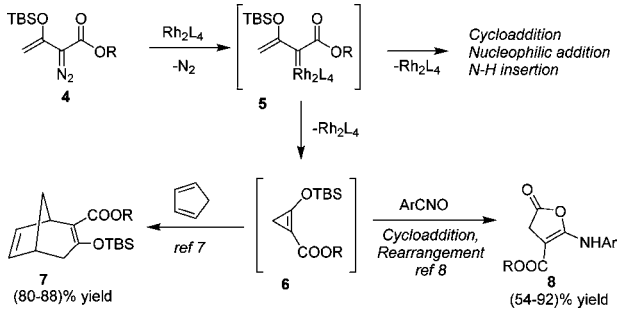


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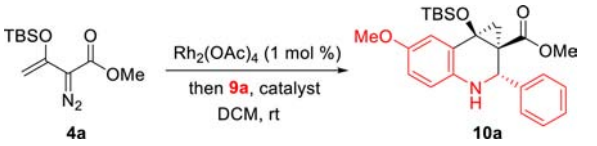
Table 1. Catalyst Screening and Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	time (h)	dr (*anti*/*syn*)[b]	yield (%)[c]
1	none	12	–	0
2	$Sc(OTf)_3$ (5)	5	>20:1	75
3	$Sn(OTf)_3$ (5)	5	>20:1	50
4	$Zn(OTf)_2$ (5)	5	>20:1	69
5	$Cu(OTf)_2$ (5)	5	>20:1	45
6	TMSOTf (10)	5	>20:1	56
7	TFA (20)	5	–	0
8	TfOH (5)	3	>20:1	60
9[d]	$Sc(OTf)_3$ (5)	5	>20:1	68
10[e]	**$Sc(OTf)_3$ (5)**	**2**	**>20:1**	**92**

[a] A solution of **4a** (0.6 mmol) and 1 mol % $Rh_2(OAc)_4$ in 2 mL of DCM was stirred at 0 °C for 30 min and then for 10 min at rt. Imine **9a** (0.5 mmol) and the stated mol % Sc(OTf) were then added to the reaction solution at 0 °C and stirred for the stated time. [b] Diastereoselectivity was determined by ^{1}H NMR spectroscopic analyses of the unpurified reaction mixture. [c] Yield of isolated product. [d] Reaction was run with 4 Å MS (150 mg). [e] Reaction was carried out at 0 °C. TFA = trifluoroacetic acid. PMP = *p*-methoxyphenyl.

imines and donor−acceptor cyclopropenes that are generated from $Rh_2(OAc)_4$-catalyzed dinitrogen extrusion from enoldiazoacetates. This highly regio- and diastereoselective transformation provides direct access to functionalized cyclopropane-fused tetrahydroquinolines and, with cyclopropane ring-opening, to benzazepine structural units.

Our investigation began with reactions of enoldiazoacetate **4a** using 1 mol % of $Rh_2(OAc)_4$ to generate the donor−acceptor cyclopropene intermediate **6** (R = Me) followed by addition of anisylbenzaldimine **9a**.

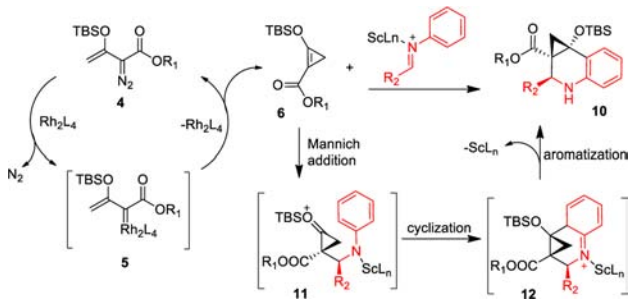
Tetrahydroquinoline **10a** was isolated as a single diastereoisomer in 75% yield following addition of 5.0 mol % of $Sc(OTf)_3$. No reaction occurred between cyclopropene **6** and imine **9a** in the absence of $Sc(OTf)_3$. The stereochemistry of **10a** with ester and phenyl groups trans was determined by single crystal X-ray analysis (see Supporting Information). Encouraged by this result, we optimized the reaction conditions by surveying a variety of Lewis and Brønsted acid catalysts (Table 1, entries 3−8). However, none of the surveyed catalysts gave a higher yield of **10a** than did $Sc(OTf)_3$, and only $Zn(OTf)_2$ give a comparable yield. Triflic acid gave a moderate yield of product, but trifluoroacetic acid did not catalyze product formation even at 20 mol %. Therefore, $Sc(OTf)_3$ was the catalyst of

(9) (a) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656–670. (b) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721–2750. (c) Bello, D.; Ramon, R.; Lavilla, R. *Curr. Org. Chem.* **2010**, *14*, 332.

choice, and 4 Å MS was used as an additive to remove any traces of water in the reaction mixture, although without improving product yield (entry 9). Observing that addition of $Sc(OTf)_3$ to the reaction solution at room temperature caused its color to change from light yellow to almost black within 10 min and immediately caused the temperature of the reaction flask to increase, the reaction temperature was lowered to 0 °C. Under these conditions the reaction was complete in 2 h, and **10a** was isolated in 92% yield.

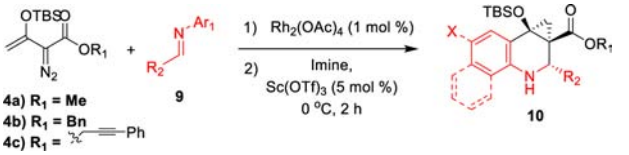
A stepwise mechanism[9b,10] for the formation of the cyclopropane-fused tetrahydroquinolines is outlined in Scheme 3. Dirhodium(II) catalyzed dinitrogen extrusion from enoldiazoacetate **4** forms intermediate metal enol carbene **5** that undergoes intramolecular cyclization to form donor−acceptor cyclopropene **6**. Mannich addition from **6** to the $Sc(OTf)_3$ activated imine generates the reactive oxonium ion **11** that undergoes intramolecular electrophilic aromatic addition (**11**→**12**) to provide the cyclopropane-fused tetrahydroquinoline **10**. Alternatively, the cycloadditions between cyclopropene **6** and $Sc(OTf)_3$ activated imines could proceed in a concerted fashion to generate the *exo*-product **10**.[10c]

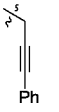
Scheme 3. Proposed Mechanism



The generality of the Povarov reaction with donor−acceptor cyclopropenes **4a**−**6a** was evaluated under these optimized conditions with imines **9a**−**9p**, and the results are reported in Table 2. The reaction provides excellent yields and diastereoselectivities toward aromatic substitution with aryl groups for R_2 having both electron-donating and moderately electron-withdrawing substituents, as well as those with ortho-, meta-, and para-halide substitution (Table 2, entries 2−8). Furyl and styryl groups as R_2 also give Povarov products with high yields (entries 9−10). As indicated by the result with R_2 = isobutyl (entry 11), an alkyl substituent is only moderately limiting on this reaction with a slight decrease in yield for **10k** and 10:1 diastereoselectivity. Substituents on the *N*-aryl group (Ar_1) also showed generality in applications (entries 13−16), and the *p*-nitro group had the expected decrease in reactivity toward cyclization that resulted in lower product yield. Different ester alkyl groups for R_1 also provide Povarov products in high yield and diastereoselectivity (entries 17 and 18).

Table 2. Povarov Reaction with in Situ Generated Donor−Acceptor Cyclopropene[a]



entry	R_1	Ar_1	R_2	**10**	dr (anti/syn)[b]	yield (%)[c]
1	Me	4-$MeOC_6H_4$	C_6H_5	**10a**	>20:1	92
2	Me	4-$MeOC_6H_4$	2-naphthyl	**10b**	>20:1	92
3	Me	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**10c**	>20:1	88
4	Me	4-$MeOC_6H_4$	4-BrC_6H_4	**10d**	>20:1	82
5	Me	4-$MeOC_6H_4$	3-BrC_6H_4	**10e**	>20:1	83
6	Me	4-$MeOC_6H_4$	2-ClC_6H_4	**10f**	>20:1	75
7	Me	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	**10g**	>20:1	90
8	Me	4-$MeOC_6H_4$	4-$CH_3C_6H_4$	**10h**	>20:1	87
9	Me	4-$MeOC_6H_4$	2-furyl	**10i**	>20:1	90
10	Me	4-$MeOC_6H_4$	styryl	**10j**	>20:1	81
11	Me	4-$MeOC_6H_4$	isobutyl	**10k**	10:1	75
12	Me	4-$MeOC_6H_4$	COOEt	**10l**	>20:1	45
13	Me	C_6H_5	C_6H_5	**10m**	>20:1	84
14	Me	4-ClC_6H_4	C_6H_5	**10n**	>20:1	85
15	Me	4-$NO_2C_6H_4$	C_6H_5	**10o**	>20:1	35
16	Me	1-naphthyl	C_6H_5	**10p**	>20:1	81
17	Bn	4-$MeOC_6H_4$	C_6H_5	**10q**	>20:1	80
18		4-$MeOC_6H_4$	4-BrC_6H_4	**10r**	>20:1	91

[a] Reactions were carried out on a 0.5 mmol scale: A solution of **4a** (0.6 mmol) and 1 mol % $Rh_2(OAc)_4$ in 2 mL of DCM was stirred at 0 °C for 30 min, then 10 min at rt. Imine **9** (0.5 mmol), and 5 mol % $Sc(OTf)_3$ was added to the reaction at 0 °C and stirred for 2 h. [b] Diastereoselectivity was determined by ^1H NMR spectroscopic analyses of the unpurified reaction mixture using the proton signal of the propyl group. [c] Yield of isolated product after chromatography.

Replacing the aryl substituent with a methyl ester (COOMe) group, however, provided **10l** in only 45% isolated yield (entry 12). With the expectation that the reaction occurs as a stepwise process,[9b,10] we hypothesized that the low yield of **10l** is due to coordination of the carbonyl group of the ester with the acid catalyst **13**, reducing the nucleophilicity of the nitrogen-activated aromatic ring toward addition to the oxonium ion **14** (Scheme 4).

Cyclopropenes have enhanced reactivity over unstrained alkenes in cycloaddition reactions,[11] but this is the first example of their viability for the Povarov reaction.[9] Access to donor−acceptor cyclopropenes, which are available through

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Scheme 4. Proposed Lewis acid coordinating to **10l**

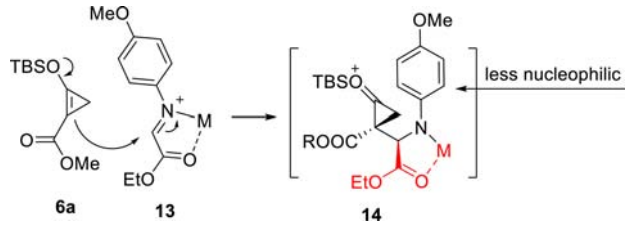
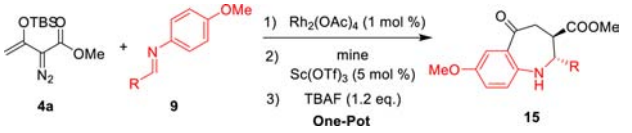


Table 3. One-Pot Synthesis of 1*H*-Benzazepines[a]



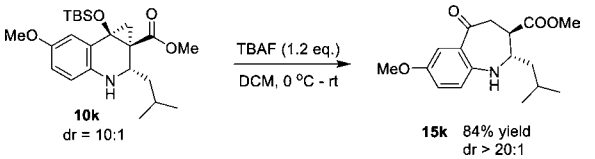
entry	R	15	dr (*anti*/*syn*)[b]	yield (%)[c]
1	C_6H_5	**15a**	18:1	71
2	4-$MeOC_6H_4$	**15b**	17:1	78
3	2-naphthyl	**15c**	13:1	75
4	3-BrC_6H_4	**15d**	9:1	70

[a] Reactions were carried out on a 0.5 mmol scale: A solution of **4a** (0.6 mmol) and 1 mol % $Rh_2(OAc)_4$ in 2 mL of DCM was stirred at 0 °C for 30 min and then for 10 min at rt. Imine **9** (0.5 mmol) and 5 mol % $Sc(OTf)_3$ were added sequentially to the reaction solution at 0 °C and stirred for 2 h, then TBAF (1.2 equiv) was added, and the resulting solution was stirred for 2 h. [b] Diastereoselectivity was determined by ^1H NMR spectroscopic analyses of the unpurified reaction mixture using the α-hydrogen of the ester group. [c] Yield of isolated product after chromatography. PMP = *p*-methoxyphenyl. TBAF = tetra-*n*-butylammonium fluoride.

dirhodium carboxylate catalyzed reactions with enoldiazoacetates,[12] provides added versatility for these processes.

The product from the Povarov reaction of **4** with imines contains the tetrahydroquinoline unit that is fused with a donor–acceptor cyclopropane. The donor–acceptor cyclopropane functionality provides the structural framework for further transformations.[13] Tetrahydroquinoline **10k** underwent ring opening when treated with tetrabutylammonium fluoride (TBAF)[14] to generate 1*H*-benzazepine **15k** in high yield and diastereoselectivity (Scheme 5). 1*H*-Benzazepines **15a**–**15d** were obtained in a one-pot procedure starting with enoldiazoacetate **4a** and imines (Table 3). Diastereoselectivity for the formation of **15** was determined by the protonation of the ester enolate intermediate which forms the more stable *trans*-products.[5a]

Scheme 5. Benzazepine Synthesis



In conclusion, we have developed a novel regio- and diastereoselective Lewis acid catalyzed Povarov reaction between imines and donor–acceptor cyclopropenes that provides direct access to functionalized cyclopropane-fused tetrahydroquinoline and 1*H*-benzazepine derivatives. This is an efficient, clean, and atom-economic transformation since the cyclopropenes are catalytically generated in situ from enoldiazoacetates, and nitrogen gas is the only byproduct. Conversion of **10** to 1*H*-benzazepine derivatives occurs in good yield under mild conditions and is linked to the Povarov process through a one-pot process.

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Supporting Information Available. General experimental procedures, the X-ray crystal structure of **10r**, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.