Asymmetric Catalysis

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Enantioselective Intramolecular C–H Insertion of Donor- and Donor/Donor-Carbenes by a Nondiazo Approach

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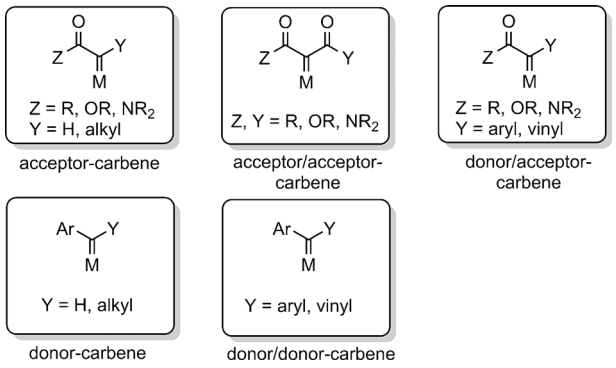
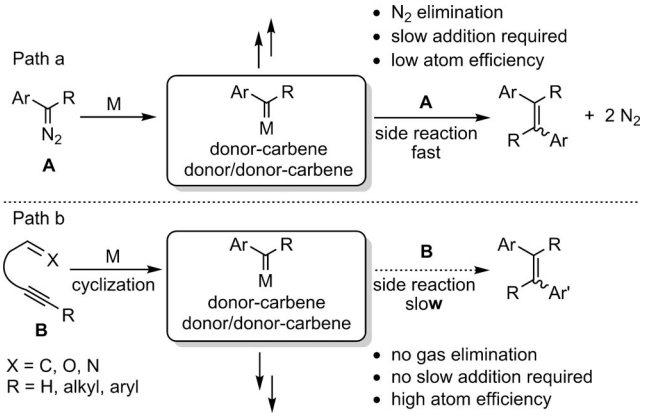
Abstract: *The first enantioselective intramolecular C–H insertion and cyclopropanation reactions of donor- and donor/donor-carbenes by a nondiazo approach are reported. The reactions were conducted in a one-pot manner without slow addition and provided the desired dihydroindole, dihydrobenzofuran, tetrahydrofuran, and tetrahydropyrrole derivatives with up to 99 % ee and 100 % atom efficiency.*

In the past decades, few intermediates have attracted as much interest as carbenes.[1] The versatile reactivities of carbenes, especially metal carbenoids, make it one of the most important and useful intermediates since it was first discovered. Among different carbene sources, diazo compounds are one of the most commonly used carbene precursors. The diazo compounds can be classified into five types:[2] acceptor-carbene, acceptor/acceptor-carbene, donor/acceptor-carbene, donor-carbene and donor/donor-carbene (Scheme 1). Although great achievements in both the theories and technologies of carbene chemistry by a diazo approach have been made in the past century, most work has been focused on the transformations of acceptor-, donor/acceptor-, and acceptor/acceptor-carbenes for their relatively good stability.[1,2] In comparison, fewer examples have been reported for donor- and donor/donor-carbenes because of safety (potential explosiveness) and practicality (easy dimerization) problems associated with the diazo compounds (Scheme 2, path a).[3–5]



Scheme 1. Different types of metal carbenoids.



Scheme 2. Carbene chemistry based on different approaches.

To meet these challenges, the reactions were typically conducted on small scale and the diazo compounds were added slowly, whereas these requirements severely limit the further application of the donor- and donor/donor-carbenes.

To solve the inherent disadvantages of the diazo chemistry, a more promising trend has been to move away from a traditional diazo-based carbene strategy but focus on a nondiazo approach instead. Recently, transition-metal-catalyzed activation and cyclization reactions of alkynes by metal carbenoid intermediates have become a very popular alternative pathway to realize different carbene-transfer reactions (Scheme 2, Path b).[6] Such a strategy would be particularly useful for donor- and donor/donor-carbenes because it is safe (no gas emission), practical (no slow addition required), and highly atom-efficient (up to 100 % atom efficiency).

As part of our continuous efforts to develop safe and practical carbene chemistry based on enynals/enynones as efficient carbene precursors,[7,8] we report herein the first enantioselective intramolecular C–H insertion and cyclopropanation reactions of donor- and donor/donor-carbenes by a nondiazo approach. As dihydroindole and dihydrobenzofuran are core structures of a variety of natural and bioactive compounds, our first target was to explore C–H insertion reactions of donor/donor-metal carbenoids, which are gen-

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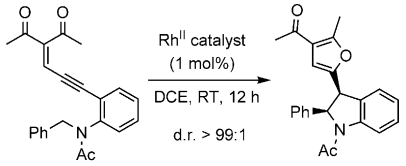
erated from the cyclization of enynones (**1**; see Table 1), thus giving rise to a range of enantioenriched dihydroindoles and dihydrobenzofurans.

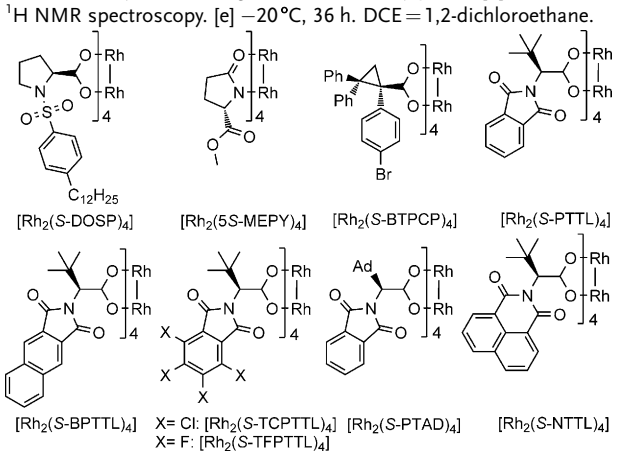
We optimized the C–H insertion reaction conditions by using the enynone **1a**, tethered to a N-benzylacetamide, as a standard substrate (Table 1). The desired dihydroindole **2a** could be obtained in quantitative yield and with larger than 99:1 diastereoselectivity when the reaction was conducted at

Table 1: Optimization of the reaction conditions.[a]



Entry	Rh^{II}	Solvent	Yield [%][b]	*ee* [%][c]
1	$[Rh_2(OPiv)_4]$	DCE	99	–
2	$[Rh_2(S\text{-DOSP})_4]$	DCE	99	22
3	$[Rh_2(S\text{-BTPCP})_4]$	DCE	8[d]	−66
4	$Rh_2(5S\text{-MEPY})_4]$	DCE	21[d]	4
5	$[Rh_2(S\text{-PTTL})_4]$	DCE	99	70
6	$[Rh_2(S\text{-BPTTL})_4]$	DCE	99	85
7	$[Rh_2(S\text{-TCPTTL})_4]$	DCE	99	38
8	$[Rh_2(S\text{-TFPTTL})_4]$	DCE	99	75
9	$[Rh_2(S\text{-PTAD})_4]$	DCE	99	94
10	$[Rh_2(S\text{-NTTL})_4]$	DCE	99	56
11	$[Rh_2(S\text{-PTAD})_4]$	DCM	99	88
12	$[Rh_2(S\text{-PTAD})_4]$	toluene	99	73
13	$[Rh_2(S\text{-PTAD})_4]$	hexane	90	80
14[e]	$[Rh_2(S\text{-PTAD})_4]$	DCE	99	97

[a] Reaction conditions: $[Rh_2L_4]$/**1a** = 0.002: 0.2 (mmol) in 2 mL of solvent at 25 °C. [b] Yield of isolated product. [c] The *ee* value of **2a** was determined by HPLC using a chiral stationary phase. [d] Determined by ^{1}H NMR spectroscopy. [e] −20 °C, 36 h. DCE = 1,2-dichloroethane.

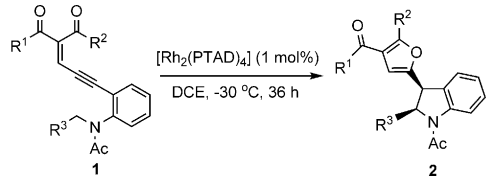


room temperature with 1 mol% $[Rh_2(OPiv)_4]$ in a one-pot manner (Table 1, entry 1). Dirhodium N-sulfonylprolinates such as $[Rh_2(S\text{-DOSP})_4]$ resulted in high yield, but with only 22% *ee* (entry 2). Dirhodium triarylcyclopropane carboxylate catalysts such as $[Rh_2(S\text{-BTPCP})_4]$ led to higher enantioselectivity (−66% *ee*), but much lower reactivity (entry 3). The result using the rhodium(II) carboxamide catalyst $[Rh_2(5S\text{-MEPY})_4]$ was discouraging (entry 4). To our delight, the phthalimide-based catalysts proved to be better choices for the reaction, thus resulting in the desired **2a** in quantitative yield and with enantioselectivities within the 38–94% range (entries 5–9). For example, the enantioselectivity reached to 70% when $[Rh_2(S\text{-PTTL})_4]$ was applied as the catalyst (entry 5). The use of a bulkier dirhodium catalyst, $[Rh_2(S\text{-BPTTL})_4]$, further increased the enantioselectivity to 85% (entry 6). Electron-deficient dirhodium catalysts, $[Rh_2(S\text{-TCPTTL})_4]$ and $[Rh_2(S\text{-TFPTTL})_4]$, gave 38 and 75% *ee*, respectively (entries 7and 8). $[Rh_2(S\text{-PTAD})_4]$ gave the highest enantioselectivity of 94% *ee* (entry 9). N-naphthaloyltethered chiral dirhodium tetracarboxylates such as $[Rh_2(S\text{-NTTL})_4]$ performed good activity but with only moderate enantioselectivity (entry 10). In the tested solvents, DCE proved to be the optimal one (entries 11–13). Lowering the reaction temperature to −20 °C further improved the enantioselectivity to 97% *ee* (entry 14).

Based on the optimized reaction conditions (Table 1, entry 14), the substrate scope of the asymmetric intramolecular C–H insertion was then examined. It was shown that the catalytic process could be successfully applied to different enynone substrates bearing N-alkylacetamide side chains (Table 2). For example, in addition to **1a**, various enynone derivatives (**1**) containing N-arylmethylacetamides could be effectively converted into the desired dihydroindoles **2** with excellent enantioselectivities (91–99% *ee*; **2a**–**l**). The yields were typically higher than 90% for most substrates. The substrates with electron-rich aryl groups have higher reactivity, thus furnishing the dihydroindole products **2a**–**e** in almost quantitative yields. This C–H insertion reaction could be easily scaled up to gram scale without the loss of the yield and enantioselectivity by using only 0.1 mol% catalyst, which afforded the product **2f** in 96% yield and 99% *ee*. The functional groups MeO, NO_2, CN, and ester were all well-tolerated (**2e**, **2j**, **2k**, **2l**). Furthermore, the enynone with N-alkylacetamide also served as a substrate, thus affording the desired product **2m** in good yield, but both the diastereo- and enantioselectivity fell significantly (1:1 d.r., 71% *ee*). Moreover, enynones with different substituents on the carbonyl groups were also suitable substrates for this transformation, and led to the dihydroindoles **2n** and **2o** in 94 and 80% *ee*, respectively.

In addition to the enynones with an N-alkylacetamide substituent, we also investigated the C–H insertion of enynones having an ether side chain, thus producing the corresponding chiral dihydrobenzofuran or tetrahydrofuran (Table 3). Like the N-alkylacetamide enynones **1**, the ether counterparts also underwent the C–H insertion reaction smoothly, thus producing the corresponding products in good yields (65–99%), whereas the ether counterparts were more sensitive to the electronic and steric factors of R^3. For example, the enynones **1** tethered to an electron-deficient benzylic ether functioned better than an electron-rich one (**2aa**–**ae**). While enynones with bulkier benzylic ether moieties exhibited higher enantioselectivity (**2af**–**ak**). Pentafluorobenzylic ether, which is an extremely electron-deficient substrate, showed excellent stereo- and enantioselectivity but with somewhat lower reactivity (**2aj**). In addition to benzylic ethers, an allylic ether, aliphatic ether, and even

Table 2: Synthesis of dihydroindoles.[a]



2a 99%, > 99:1 d.r., 97% *ee*

2b 94%, > 99:1 d.r., 96% *ee*

2c 99%, > 99:1 d.r., 97% *ee*

2d 99%, > 99:1 d.r., 98% *ee* (44 h)

2e 99%, > 99:1 d.r., 91% *ee*

2f 99%, > 99:1 d.r., 99% *ee* (96%, > 99:1 d.r., 99% *ee*)[b] (1.1 g scale, 0.1 mol%, 72 h)

2g 99%, > 99:1 d.r., 97% *ee*

2h 95%, > 99:1 d.r., 98% *ee*

2i 84%, > 99:1 d.r., 97% *ee* (2 mol%)

2j 99%, > 99:1 d.r., 96% *ee* (RT, 12 h)

2k 99%, > 99:1 d.r., 99% *ee* (RT, 24 h)

2l 88%, > 99:1 d.r., 99% *ee* (48 h)

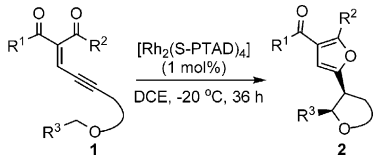
2m[c] 83%, 1:1 d.r., 71% *ee* (60 °C, 24 h)

2n 88%, > 99:1 d.r., 94% *ee* (44 h)

2o[d] 74%, > 99:1 d.r., 80% *ee* (24 h)

[a] $[Rh_2(PTAD)_4]/\mathbf{1} = 0.002$: 0.2 (mmol) in 2 mL of DCE. Yield is that of isolated product. [b] 0 °C. [c] Determined by ^{1}H NMR spectroscopy. [d] The *E*-configured enynone **1** was used.

Table 3: Synthesis of dihydrobenzofurans or tetrahydrofurans.[a]



2aa 99%, 98:2 d.r., 85% *ee* (-30 °C, 24 h)

2ab 99%, 97:3 d.r., 72% *ee* (-30 °C, 24 h)

2ac 99%, 96:4 d.r., 85% *ee* (-30 °C, 24 h)

2ad 99%, 98:2 d.r., 90% *ee* (-30 °C, 24 h)

2ae 99%, > 99:1 d.r., 90% *ee* (-30 °C, 48 h)

2af 99%, 97:3 d.r., 89% *ee* (-30 °C, 24 h)

2ag 79%, 98:2 d.r., 92% *ee* (2 mol%, -30 °C, 48 h)

2ah 91%, 97:3 d.r., 94% *ee* (2 mol%, -30 °C, 72 h)

2ai 77%, 98:2 d.r., 98% *ee* (3 mol%, -30 °C, 72 h)

2aj 65%, 97:3 d.r., 94% *ee* (5 mol%, -10 °C, 24 h)

2ak[b] 82%, 99:1 d.r., 96% *ee* (3 mol%, -30 °, 72 h)

2al 99%, 93:7 d.r., 89% *ee* (-30 °C, 24 h)

2am 99%, 75:25 d.r., 73% *ee*[c] (-30 °C, 24 h)

2an 99%, >99:1 d.r., 64% *ee* (60 °C, 48 h)

2ao 99%, 95:5 d.r., 73% *ee* (RT, 12 h)

2ap 99%, 77:23 d.r., 61% *ee* (RT, 12 h)

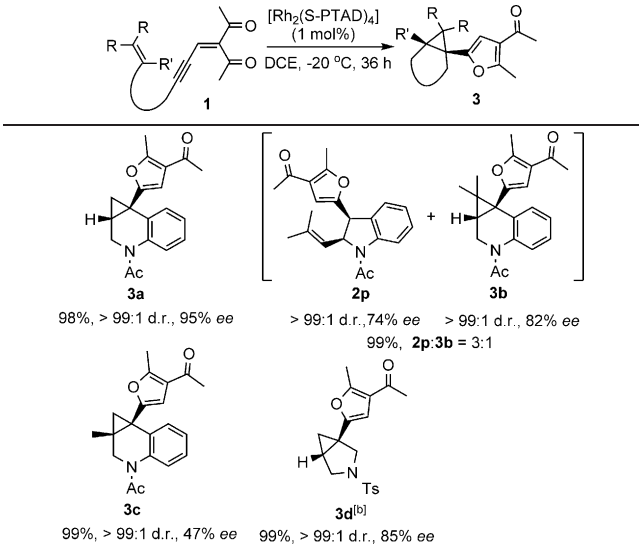
2aq 99%, 92:8 d.r., 62% *ee* (RT, 12 h)

[a] $[Rh_2(PTAD)_4]/\mathbf{1} = 0.002$: 0.2 (mmol) in 2 mL of DCE. Yield is that of isolated product. [b] The *E*-configured enynone **1** was used. [c] The *ee* value of the major isomer.

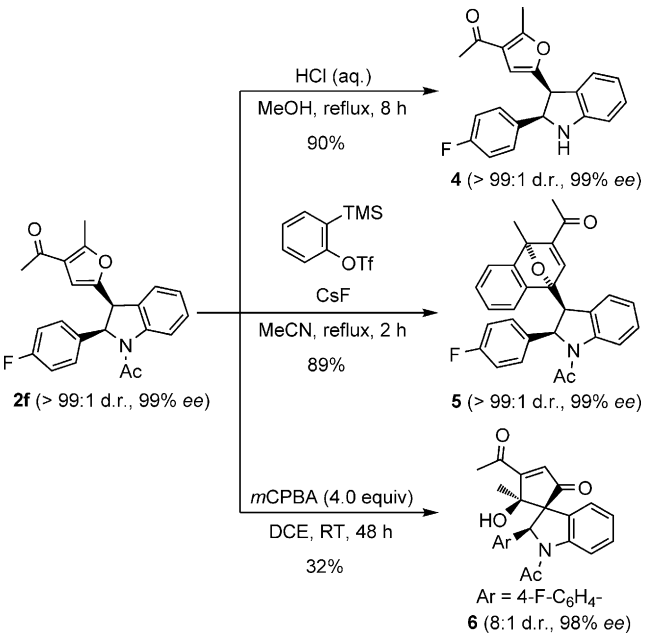
ester-containing ether also reacted smoothly in the C–H insertion process (**2al**–**an**). In the case of allylic ether, only insertion was observed with no detectable cyclopropane product (**2al**). The aliphatic ether and 2-ethoxy-2-oxoethyl ether had good reactivities but with moderate enantioselectivities (**2am**). The successful preparation of dihydroindole and dihydrobenzofuran through the insertion of a donor/donor-carbene prompted us to explore the insertion of a more challenging donor-carbene. As shown in Table 2, enynones substituted with alkyl groups at the alkynyl carbon atom, which react with the catalyst to form the donor-metal carbenoids, are also efficient in this reaction. Both benzylic and allylic ethers produced the desired tetrahydrofurans in quantitative yields, albeit with somewhat lower enantioselectivities (**2ao**–**aq**). In all cases shown in Tables 2 and 3, the reactions were conducted in a one-pot manner, and it is surprising that there were no detectable products of dimerization.

Having established the intramolecular C–H insertion as a reliable and efficient synthetic protocol, we then proceeded to develop the intramolecular cyclopropanation reactions

Table 4: Intramolecular cyclopropanation.[a]



[a] Reaction conditions: $[Rh_2L_4]$/**1** = 0.002: 0.2 (mmol) in 2 mL of DCE at −20 °C. Yield is that of the isolated product. [b] 1 mol% $[Rh_2(S\text{-BPTTL})_4]$, −30 °C, 12 h.



Scheme 3. Further transformation of **2f**. *m*CPBA = *m*-chloroperbenzoic acid, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

aimed at the cyclopropane-fused polycyclic structures. To realize this, the enynones **1**, with tethered alkenyl side chains, were then employed. As shown in Table 4, an enynone tethered to an N-allylic acetamide reacted smoothly, thus giving the desired cyclopropane **3a** in 98% yield and good selectivity. No allylic C–H insertion product was detected. Interestingly, a competition between C–H insertion and cyclopropanation occurred when 3,3-dimethyl allylic acetamide was chosen as the substrate, with the insertion product dominated. The reaction afforded the insertion product **2p** and cyclopropane product **3b**. Such results may be attributed to the steric effect of the dimethyl groups, which impeded the cyclopropanation. This proposal was supported by the results in which the sole cyclopropane **3c** was formed in quantitative yield when a less bulky substrate, 2-methyl allylic acetamide, was applied as the substrate. However, the enantioselectivity of **3c** dropped dramatically to 47%. Similarly with the insertion reactions, the cyclopropanation could be extended to a donor-carbene as well. For example, when an enynone with a nonaromatic amide side chain was utilized as the donor-carbene precursor, the desired cyclopropane **3d** was produced in quantitative yield and good selectivity by using 1 mol% $[Rh_2(S\text{-BPTTL})_4]$ as the catalyst instead.

With the C–H insertion products **2** in hand, further chemical transformations were also carried out to demonstrate the potential applications of these molecules (Scheme 3). Take **2f** as an example, for the N-acetyl group could be easily removed under acidic conditions in 90% yield. Furthermore, the furan moiety of the product is a good diene and reacted with benzyne to form the product **5** through a [4+2] cycloaddition. In the above-mentioned transformations, both the diastereo- and enantioselectivity remained unchanged. More interestingly, when **2f** was subjected to oxidation conditions with *m*CPBA as the oxidant,[9] the spirocyclopentenone **6** was formed, presumably by an oxidation/aldol reaction sequence.

In summary, we have developed the first enantioselective intramolecular C–H insertion and cyclopropanation reactions of donor- and donor/donor-carbenes by a nondiazo approach. The reactions were conducted in a one-pot manner without slow addition and provided the desired dihydroindole, dihydrobenzofuran, tetrahydrofuran, and tetrahydropyrrole derivatives with up to 99% *ee* and 100% atom efficiency. We believe that these safe and practical asymmetric C–H insertion and cyclopropanation reactions of the donor- and donor/donor-carbenes by a non-diazo approach, without the formation of the dimerization alkene side-products and the requirement of slow addition, should provide appealing methodologies for organic synthesis. Investigations on further applications of these reactions are underway in our laboratory.

Acknowledgments

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Keywords: asymmetric catalysis · carbenes · heterocycles · insertion · rhodium

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Communications

Asymmetric Catalysis

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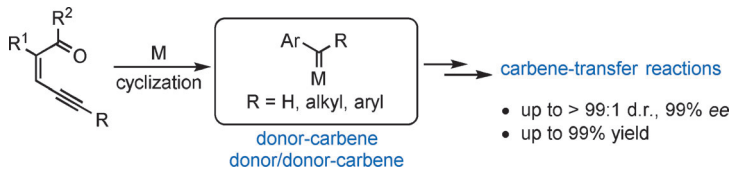
Enantioselective Intramolecular C–H Insertion of Donor- and Donor/Donor-Carbenes by a Nondiazo Approach



Generous donor: Enantioselective intramolecular C–H insertion and cyclopropanation reactions of donor- and donor/donor-carbenes by a nondiazo approach are reported. The reactions were conducted in a one-pot manner without slow addition and provided the desired dihydroindole, dihydrobenzofuran, tetrahydrofuran, and tetrahydropyrrole derivatives with up to 99% *ee*.