Catalytic Asymmetric Solid-Phase Cyclopropanation

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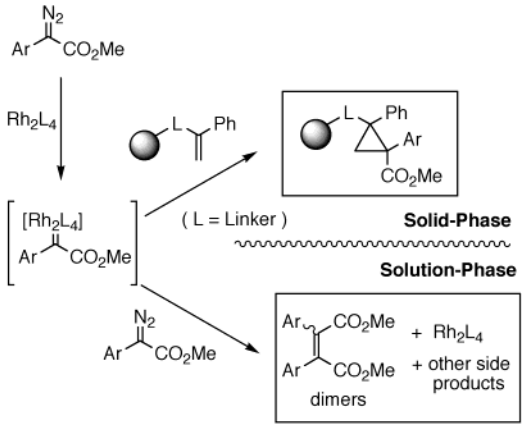
Solid-phase synthesis of small molecules has been recognized as an efficient tool to prepare chemical libraries.[1] In recent years a number of C−C bond forming reactions have been applied to solid-phase reactions.[2] A limited number of catalytic asymmetric reactions have also been applied to substrates bound to solid supports.[3] In this communication, the first example of catalytic asymmetric cyclopropanations of alkenes on solid support is described. A major advantage of this process is that the high yield of cyclopropanation can be achieved even when the alkene is used as the limiting agent.

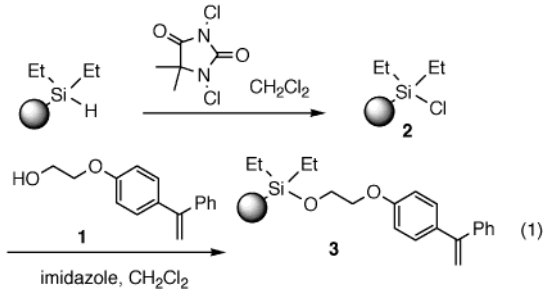
The metal-catalyzed cyclopropanation of diazo compounds has broad utility in organic synthesis.[4] One of the major challenges for efficient intermolecular cyclopropanations is the control of the high reactivity of the carbenoid intermediate.[4] Carbene dimerization is a very prevalent side reaction, and typically an excess of trapping agent and syringe pump techniques[5] are required to alleviate this problem. We have found that the carbenoids derived from aryldiazoacetates are much less prone to dimerization than the typical carbenoids derived from unsubstituted diazoacetates,[6] and Rh_2(*S*-DOSP)$_4$[7] is an exceptional chiral catalyst for aryldiazoacetates.[8] In a recent study, however, directed toward the asymmetric synthesis of cyclopropyl analogues of tamoxifen,[9] we found that carbene dimerization with an aryldiazoacetate could not be completely suppressed. The separation difficulties associated with this reaction led us to consider a solid-phase approach whereby an elaborate trapping agent could be used as the limiting agent. Our studies to develop such an approach are described here.

An earlier attempt has been made to limit the problems of carbene dimerization by placing an unsubstituted diazoacetate on a solid support.[10] $Rh_2(OAc)_4$-catalyzed decomposition of the diazoacetate on the solid support in the presence of 20 equiv of alkyne resulted in the formation of a cyclopropene in 30% yield after cleavage of the linker.[10] In our case, we wished to have the alkene trap as the limiting reagent and so it was placed on the solid support (Scheme 1). If the carbenoid were sufficiently selective, high conversion to the cyclopropane would be possible by using an excess of the carbenoid source. Any carbene side products would remain in the liquid phase and would be readily removed by filtration with appropriate solvents.

Scheme 1



As shown in eq 1, a resin-bound olefin **3** was prepared from the corresponding alcohol **1** and a polystyrene resin with a silicon linker (PS-DES-SiH resin, Argonaut technologies). The silane group in PS-DES-SiH resin was chlorinated,[11] and resin **1** was reacted with a 3-fold excess of olefin **2** to give **3**. A small portion of resin **3** was treated with HF-pyridine, and the olefin loading in resin **3** was estimated based on the crude weight of olefin **2**. The range of the loading level was 0.83−1.0 mmol/g.



To optimize the stoichiometry of the phenyldiazoacetate relative to the olefin in resin **3**, Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation was conducted with 3 and 5 equiv of methyl phenyldiazoacetate (**4a**) relative to the olefin in resin **3**. Also, samples of resin **3** with different loading levels of alkene were examined to determine the reproducibility of the reaction. When 3 equiv of the diazo compound was used, the conversion varied from 75 to 97% (and a significant amount of olefin **2** was recovered (3−14%)). However, 5 equiv of the diazo was found to be sufficient to give quantitative conversion (>99%) of the olefin (Table 1). None of the olefin was detected in the ^{1}H NMR of the crude mixture after treating the resin with HF-pyridine. The same reaction conditions, with 5 equiv of ethyl diaozacetate (EDA), gave a poor conversion of olefin (35%). Even with 50 equiv of EDA the conversion of olefin was only 54% and the yield of cyclopropanation was only 8%. The contrasting results obtained with phenyldiazoacetate and EDA demonstrate the clear advantages of using the more chemoselective carbenoid.[12] The solid-phase cyclopropanation reaction between phenyldiazoacetate and resin-bound olefin **3** dispalys almost identical stereoselectivities (diastereo- and enantioselectivities) to those obtained in the corresponding reaction in solution phase. The diastereomer ratio of the cyclopropane **5a**

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(7) Rh_2(S-DOSP)$_4$ is tetrakis[*N*-[4-dodecylphenyl)sulfonyl]-(*S*)-prolinato]-dirhodium.

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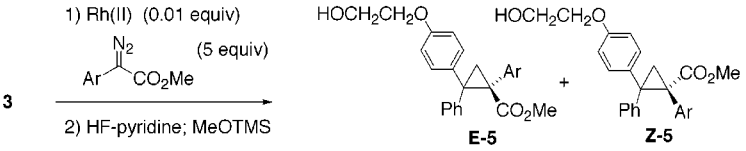
Table 1. Asymmetric Cyclopropanation on Solid Phase



entry		Ar	Rh_2(*S*-DOSP)$_4$ conversion of **3**, %	yield , %[b]	E:Z[c]	ee, % of **E-5**	Rh_2(TPA)$_4$ conversion of **3**	yield, %[b]	E:Z[c]
1	**a**	Ph	>99[a]	93	85:15	91	94[d]	88	82:18
2	**b**	2-Naphthyl	>99[a]	83	88:12	89	98	82	83:17
3	**c**	4-CH_3-C_6H_4	>99[a]	92	87:13	93	98	85	84:16
4	**d**	4-CH_3O-C_6H_4	>99[a]	96	88:12	88	97	67	82:18
5	**e**	4-CF_3-C_6H_4	52	16	75:25	86	89	62	77:23
6	**f**	4-Cl-C_6H_4	91	59	86:14	92	98	81	80:20
7	**g**	4-Br-C_6H_4	99	87	86:14	91	98	91	81:19

[a] Olefin was not detected in ^{1}H NMR of the crude mixture. [b] Determined by ^{1}H NMR with DMAP as an internal standard. [c] Determined by ^{1}H NMR of the crude mixture. [d] 3 equiv of methyl phenydiazoacetate was used.

prepared under solid-phase conditions was 84:16 favoring the trans isomer. The enantiomeric excess of the major diastereomer was 91% ee.[13]

To determine the range of the solid-phase chemistry, the effect of substituents on the aryldiazoacetate was examined. Two dirhodium catalysts were used, Rh_2(*S*-DOSP)$_4$[7] and Rh_2(triphenylacetate)$_4$ [Rh_2(TPA)$_4$].[14] The conversion of olefin **3** and the yield of cyclopropanes **4a**−**g** are shown in Table 1. With Rh_2(*S*-DOSP)$_4$, aryldiazoacetates with an electron-rich aryl group gave quantitative conversion of the olefin (entries 1−4), and the cyclopropanes were obtained in good to high yields (83−96%). In contrast to the electron-rich aryldiazoacetates, electron-deficient aryldiazoacetates gave significantly lower conversions of the olefin with Rh_2(*S*-DOSP)$_4$ (entries 5 and 6). 4-CF_3-phenyldiazoacetate gave only 52% conversion of the olefin, and the yield of cyclopropanation product **4e** was poor (16%). With 4-chlorophenyldiazoacetate, the conversion of the olefin was 91% and the yield of the cyclopropane **4f** was moderate (59%). The low conversion of the olefin with 4-CF_3- and 4-Cl-phenyldiazoacetates may suggest that competing side reactions (e.g. carbene dimerization) are more prevalent when the carbenoid is more electron-deficient. The cyclopropanations with Rh_2(TPA)$_4$ gave consistently good to high conversions of the olefin (89−98%). Similar to the results obtained with Rh_2(*S*-DOSP)$_4$, high conversions of olefin were achieved with electron-rich aryldiazoacetates (entries 1−4). Quite interestingly, even with 4-CF_3-phenyldiazoacetate, the conversion is still good (89%), and with 4-Cl-phenyldiazoacetate the conversion was nearly quantitative. These results suggest that the carbenoids derived from the Rh_2(TPA)$_4$-catalyzed reactions are more chemoselective than those derived from the Rh_2(*S*-DOSP)$_4$-catalyzed reactions.

The diastereo- and enantioselectivities of the cyclopropanation reactions are also summarized in Table 1. Except for the results obtained with 4-CF_3-phenyldiazoacetate (entry 5), narrow ranges of diastereomer ratios were obtained. The diastereomer ratios were 85:15 to 88:12 with Rh_2(*S*-DOSP)$_4$ and were 80:20 to 84:16 with Rh_2(TPA)$_4$. The enantiomeric excess was also in a narrow range (86−93% ee). Interestingly, an electron-rich diazo (4-MeO-phenyldiazoacetate, entry 4) and an electron-deficient diazo (4-CF_3-phenyldiazoacetate, entry 5) gave similar enantiomeric excess. These results may suggest that the electronic property of the aryldiazoacetate had no significant effect on the enantioselectivity.

In summary, we have developed an effective solid-phase catalytic asymmetric cyclopropanation in which a trapping agent (olefin) can be used as the limiting agent.[15] Excellent conversions of olefin on a solid support were achieved with 5 equiv of electron-rich aryldiazoacetates and a catalytic amount of Rh_2(*S*-DOSP)$_4$ or Rh_2(TPA)$_4$. High enantiomeric excesses of the cyclopropanes were obtained in these solid-phase reactions, and the stereoselectivities are comparable to those obtained in solution-phase reactions. Because it is possible to prepare a variety of olefins such as **3** on the solid phase, our method would be a useful tool for constructing a library of aryl-substituted cyclopropane derivatives. Further studies are in progress to develop a parallel synthesis of tamoxifen analogues with this solid-phase cyclopropanation as a key step.

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Supporting Information Available: Experimental data for **1**, **3** and **5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) In the corresponding cyclopropanation of the chloro derivative of **1** with phenyldiazoacetate **4a** in solution phase (CH_2Cl_2 as solvent), the diastereomer ratio for **7** was 83:17, and the enantiomeric excess of the major diastereomer was 90% ee.

(14) Rh_2(TPA)$_4$ was used as an achiral catalyst instead of the traditional Rh_2(OAc)$_4$ because the equivalent solution-phase cyclopropanations were cleaner when catalyzed with Rh_2(TPA)$_4$ than with Rh_2(OAc)$_4$.

(15) In solution-phase competition studies it was found that 1,1-diphenylethylene was 2.5 times less reactive than styrene in reaction with **3a**. Thus, it is expected that this chemistry can be extended at least to various electron-rich alkenes.