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Catalytic Asymmetric C−H Activation of Alkanes and Tetrahydrofuran

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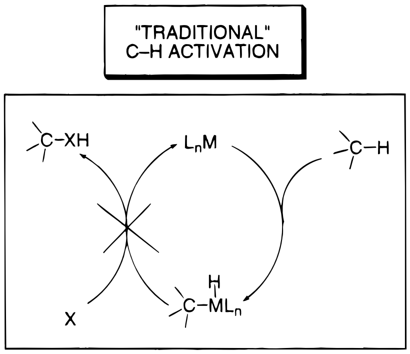
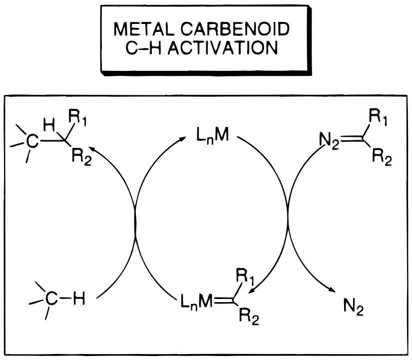
Abstract: Rhodium carbenoids derived from methyl aryldiazoacetates are capable of effective catalytic asymmetric C−H activation of a range of alkanes and tetrahydrofuran by a C−H insertion mechanism. Dirhodium tetrakis(*S*-(*N*-dodecylbenzenesulfonyl)prolinate) (Rh_2(*S*-DOSP)$_4$) catalyzed decomposition of methyl aryldiazoacetates in the presence of alkanes results in intermolecular C−H insertions with good control of regioselectivity, diastereoselectivity, and enantioselectivity. The carbenoids derived from methyl aryldiazoacetates are considerably more chemoselective than carbenoids derived from diazoacetates. They strongly favor C−H insertions into secondary and tertiary sites. Formation of side products due to carbene dimerization is not a major problem with rhodium carbenoids derived from aryldiazoacetates.

One of the most challenging reactions in organic synthesis is the functionalization of nonactivated C−H bonds. Not only does such a reaction require an extremely reactive reagent, but also, regiochemical problems would need to be overcome. Even though there are several industrial processes for functionalization of alkanes,[1] general laboratory processes for alkane C−H activation that lead directly to carbon−carbon bond formation are limited.[2] Over the last twenty years, there has been a massive effort to achieve selective C−H activation of alkanes by the use of organometallic chemistry.[2b,3] One of the central transformations that has been used for this chemistry is the oxidative addition of highly reactive metal complexes into C−H bonds (Scheme 1).[4] The ultimate goal of this chemistry would be to develop a catalytic and asymmetric C−H activation process,[5] but unfortunately, this is an extremely difficult proposition because regeneration of the highly active organometallic species to complete the catalytic cycle is very difficult.

Scheme 1



Scheme 2



In this paper, a method will be described to achieve asymmetric intermolecular C−H activation of alkanes by using an alternative catalytic cycle (Scheme 2).[6] In this scheme a highly reactive metal carbenoid intermediate will be the species that will cause the C−H activation by insertion of a carbenoid into the C−H bond. The carbenoid will be generated from a reasonably stable metal complex that can catalyze the decomposition of a diazo compound. The driving force for the generation of the highly reactive metal-carbenoid intermediate is the formation of N_2 as a byproduct. Once the carbenoid intermediate has undergone the C−H insertion into the alkane,

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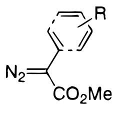
10.1021/ja994136c CCC: $19.00

the original metal complex will be formed and the catalytic cycle can continue. Even though general reviews on C−H activation of hydrocarbons[1,2a,b,3] have largely ignored carbenoid C−H insertions,[6] this process has the potential to be a practical solution to catalytic C−H activation, as long as the chemoselectivity can be controlled.

The metal-catalyzed decomposition of diazo compounds is a well-established method for the generation of reactive metal-carbenoid intermediates.[6] C−H activation by means of an intramolecular C−H insertion is a powerful synthetic method.[7] Excellent control of diastereoselectivity and enantioselectivity is possible with this chemistry. In contrast, *intermolecular C−H insertion* is not generally considered to be a synthetically useful process[8] even though numerous examples of the reaction have been reported over the years.[9] The reason for this lack of synthetic utility is that metal carbenoids are prone to dimer formation[10] and in the absence of an efficient trapping agent, the dimer formation is the dominant reaction process. Furthermore, the regioselectivity of the reported C−H insertions was not sufficient to be of general practical utility.[9]

Over the last 15 years, we[11,12,] and others[13] have explored the chemistry of a different class of metal-carbenoid intermediates which contain electron-withdrawing and electron-donating (vinyl or phenyl) groups (**1**). This class of metal-carbenoid intermediates has very different characteristics from the traditional carbenoids derived from alkyl diazoacetates. For example, its cyclopropanation chemistry is highly diastereoselective[11b,14] and by using Rh_2(*S*-DOSP)$_4$ (**2**) catalysis, its reactions are highly enantioselective.[15] Furthermore, we discovered that this type of carbenoid is much more chemoselective and less prone to dimer formation than carbenoids derived from alkyl diazoacetates.[16] This led us to consider that this class of carbenoids would be able to undergo effective intermolecular C−H insertion. In combination with Rh_2(*S*-DOSP)$_4$, this chemistry could lead to a practical catalytic asymmetric C−H activation process.



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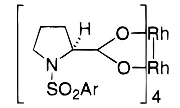

Ar = *p*-($C_{11-13}H_{23-27}$)C_6H_4

Rh_2(*S*-DOSP)$_4$

2

In our preliminary communication of this work, we reported that methyl aryldiazoacetates underwent C−H activation into cycloalkanes heated under reflux in 60−89% ee (eq 1)[17] and into tetrahydrofuran in 52−76% ee (eq 2).[17] Recently, we have demonstrated that C−H insertions of aryldiazoacetates α to nitrogen (eq 3)[18] and at allylic positions α to oxygen (eq 4)[19]

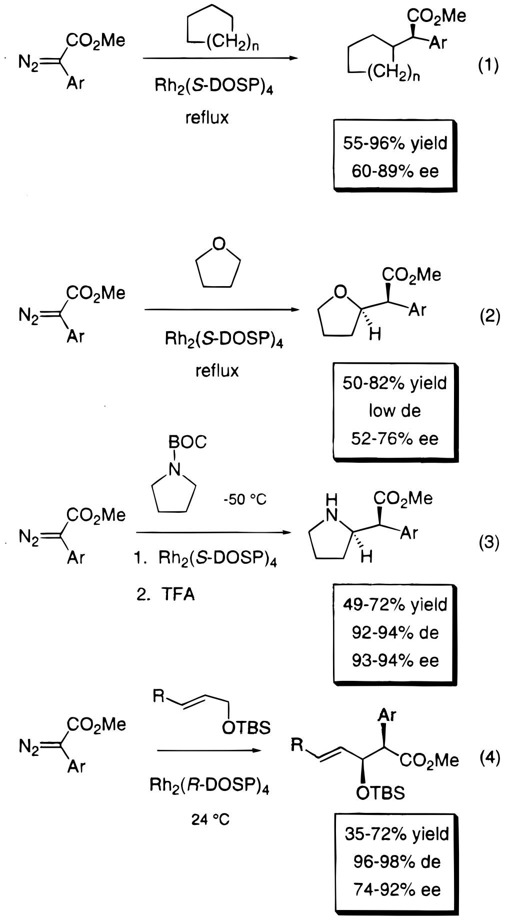

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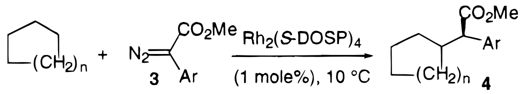
Table 1. Asymmetric C−H Activation of Cycloalkanes

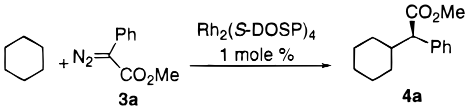


diazo	Ar	n	product	yield, %	ee, %
3a	C_6H_5	2	**4a**	80	95
3b	*p*-BrC_6H_4	2	**4b**	64	95
3c	*p*-ClC_6H_4	2	**4c**	76	94
3d	*p*-(MeO)C_6H_4	2	**4d**	23[a]	88
3e	*o*-ClC_6H_4	2	**4e**	81	90
3f	*m*-ClC_6H_4	2	**4f**	47	94
3g	*p*-CF$_{3C6}$H$_4$	2	**4g**	78	94
3h	*p*-MeC_6H_4	2	**4h**	63	93
3i	*o*-BrC_6H_4	2	**4j**	72	90
3j	*m*-BrC_6H_4	2	**4k**	62	95
3a	C_6H_5	1	**5a**	72	96
3c	*p*-ClC_6H_4	1	**5c**	70	95

[a] 3 mol % of catalyst was used.

are extremely efficient and useful transformations. In this paper we describe a systematic study exploring the scope and regiochemistry of C−H activation with various alkanes, which, of course, are very challenging substrates for this type of chemistry.

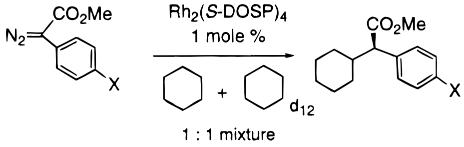
In the preliminary communication,[17] the reactions of aryldiazoacetates with cycloalkanes were carried out under reflux conditions because the yields dropped considerably when the reaction temperatures were lowered. On reexamination of the reaction of methyl phenyldiazoacetate (**3a**) with cyclohexane, we have found that if the solvent is degassed,[20] the reactions can be carried out at temperatures as low as 10 °C without an appreciable drop in yield (eq 5). In these reactions, cyclohexane is used as solvent and the aryldiazoacetate is added dropwise to Rh_2(*S*-DOSP)$_4$ over 90 min. Under these conditions, the C−H activation product **4a** is formed in 95% ee. The reaction is applicable to a range of aryldiazoacetates **3a**−**j**, and in most cases the C−H insertion products **4a**−**j** are produced in >90% ee (Table 1). Even an electron rich aromatic ring can be incorporated into the aryl diazoacetate (**3d**) although the yield of the C−H insertion product (**4d**) is considerably lower in this case (23% yield) than what was obtained when higher reaction temperatures were used (85% yield).[17] The reaction of cyclopentane with aryldiazoacetates **3a** and **3c** similarly results in the formation of the C−H insertion products **5a** and **5c** in >90% ee. The absolute configuration of **4a** was determined to be (*R*) by comparison of the optical rotation of the corresponding carboxylic acid with the literature value.[21] The absolute configuration of the other products is tentatively assigned on the assumption that the same sense of asymmetric induction occurs in all of the reactions with cycloalkanes.



(5)

Temp, °C	Conditions	Yield, %	ee, % (R)
81	Ar	83	81
50	Ar	69	88
39	Ar, degassed	81	91
24	Ar, degassed	74	92
10	Ar, degassed	80	95

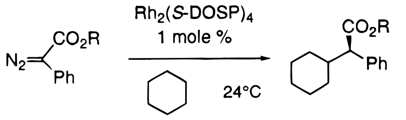
A C−H insertion process would be expected to display a considerable kinetic isotope effect.[9h,i] This was confirmed by running the reaction of aryldiazoacetates **3a**, **3c**, and **3d** with a 1:1 mixture of cyclohexane and d_{12}-cyclohexane (eq 6). From the product distribution it was determined that the kinetic isotope effect was between 2.0 and 2.1.



(6)

Diazo	X	k_H/k_D
3a	H	2.0
3c	Cl	2.0
3d	OMe	2.1

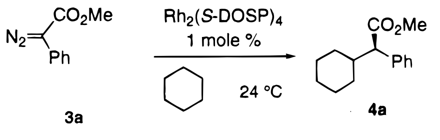
In the asymmetric cyclopropanation chemistry of alkyl vinyldiazoacetates with Rh_2(*S*-DOSP)$_4$, the enantioselectivity drops considerably on increasing the size of the alkyl group from methyl to *tert*-butyl.[15] This effect is a distinctive feature of the vinyldiazoacetate/rhodium prolinate system, because in the diazoacetate system, the highest enantioselectivity of cyclopropanation is generally obtained when a bulky ester group is used. An exploration of the effect of ester size on the C−H activation revealed that a parallel trend existed between the C−H activation and the asymmetric cyclopropanation. A slight drop in enantioselectivity occurred in the C−H activation on changing from the methyl ester **3a** to isopropyl ester **6** while with the *tert*-butyl ester **7**, the enantioselectivity for C−H insertion was only 20% ee.



(7)

Diazo	R	Product	yield, %	ee, %
3a	Me	**4a**	80	92
6	iPr	**8**	39	86
7	tBu	**9**	45	20

The standard reactions described above were carried out with 1 mol % of Rh_2(*S*-DOSP)$_4$, but lower equivalents of catalyst can be used as shown in eq 8. On using 0.1% of catalyst at 24



(8)

Rh(II), mole equiv	yield, %	ee, %
0.01	80	92
0.001	63	91
0.0001	2	70

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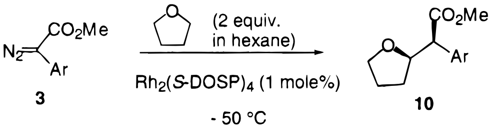
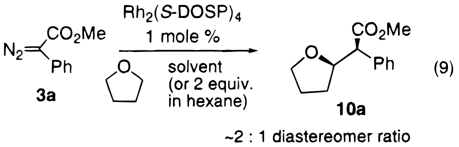
Table 2. Asymmetric C−H Activation of Tetrahydrofuran



diazo	Ar	product	combined yield, %	diastereomer ratio	ee, % (major ds)
3a	C_6H_5	**10a**	67	2.8	97
3c	*p*-ClC_6H_4	**10c**	74	2.4	98
3d	*p*-$(MeO)C_6H_4$	**10d**	56	3.4	96
3h	*p*-MeC_6H_4	**10h**	60	4.0	97
3k	2-naphthyl	**10k**	62	1.6	95

°C, the yield and enantioselectivity (91% ee vs 92% ee) of **4a** is slightly diminished. With 0.01% of catalyst, however, the reaction conversion is very low and the enantioselectivity of **4a** is considerably decreased (70% ee). A similar trend was observed in the cyclopropanation chemistry catalyzed by Rh_2(*S*-DOSP)$_4$.[15]

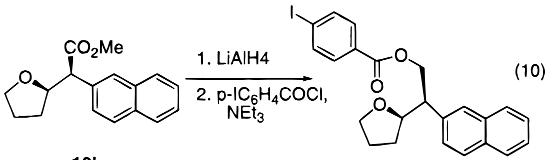
The reaction of tetrahydrofuran with aryldiazoacetates has also been optimized as illustrated in eq 9. After degassing of the solvents the reaction with tetrahydrofuran can be successfully accomplished at −50 °C and under these conditions the enantioselectivity for the formation of the C−H insertion product **10a** is 90% ee. A further improvement in enantioselectivity was possible by running the reaction in hexane with just 2 equiv of tetrahydrofuran. It is well established that the enantioselectivity for Rh_2(*S*-DOSP)$_4$ catalysis is highly sensitive to solvent effects, with nonpolar solvents being highly beneficial.[15] By using hexane as solvent the enantioselectivity for the formation of **10a** was improved to 97% ee. The observation of high yields in this reaction is remarkable because it signifies that the carbenoid is highly chemoselective, favoring reaction with the THF even in the presence of a vast excess of hydrocarbon. Under these optimized conditions, the reaction is applicable to a series of aryldiazoacetates, and in each instance, the enantioselectivity for the C−H insertion products **10** is >95% ee (Table 2).



(9)

Temp, °C	ee of **10a**, % from THF	ee of **10a**, % from hexane/THF (2 eq.)
65	72	–
24	84	92
0	88	94
-50	90	97

In the original communication, the relative stereochemistry of **10** was tentatively assigned as (2*S**,α*R**)[17] but the absolute configuration was not determined. Proof of the absolute configuration of **10k** as (2*S*,α*R*) was obtained by conversion of **10k** to crystalline **11** (eq 10), whose structure was confirmed by X-ray crystallography (Figure 1).



10k **11**

(10)

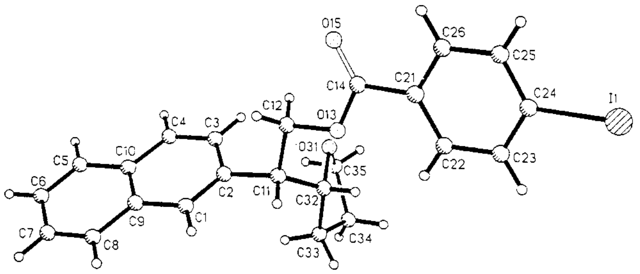
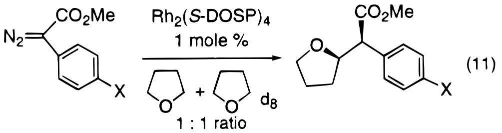


Figure 1. Absolute configuration of **11**.

The kinetic isotope effect for the C−H insertion into tetrahydrofuran was readily determined by competition experiments between tetrahydrofuran and d_8-tetrahydrofuran (eq 11). In each case, the kinetic isotope effect was greater than that for the reaction with cyclohexane, ranging from 3 to 3.2.

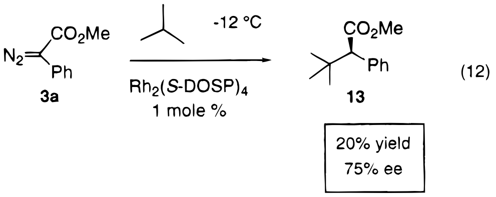


(11)

Diazo	X	k_H/k_D
3a	H	3.0
3c	Cl	3.0
3d	OMe	3.2

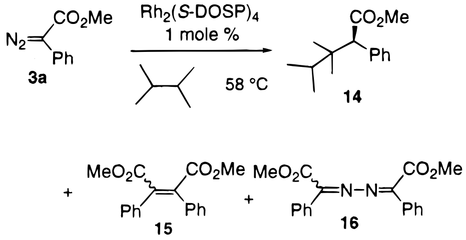
Having determined that the C−H activation was an effective process, the next series of reactions were directed toward determining the chemoselectivity of the reaction with various alkanes. From the cyclopropanation chemistry of carbenoids derived from vinyldiazoacetates, it was expected that a subtle balance of steric and electronic effects would exist. These carbenoids preferentially attack electron-rich alkenes in which charge build up in the transition step of the nonsynchronous cyclopropanation would be stabilized.[13] In a related manner, a concerted nonsynchronous C−H insertion mechanism would explain why favorable C−H insertions occur at C-2 of tetrahydrofuran. It is also well established, however, that the rhodium prolinate/vinylcarbenoid system is sterically demanding, as displayed by its inability to cyclopropanate trans alkenes.[13,15] Consequently, in the case of the C−H insertion, it was expected that the tertiary C−H bonds would be preferentially attacked on electronic grounds but steric factors might reverse this trend.

The reaction with isobutane was examined to determine the reactivity difference between primary and tertiary C−H bonds. Due to its physical properties (bp −12 °C), this is not an ideal substrate because the reaction needs to be carried out below the optimum temperatures of 10 °C or greater unless one is willing to resort to using a pressure reactor. Nevertheless, C−H insertion into the tertiary C−H bond did occur at −12 °C to form **13** in 75% ee. The yield of **13**, however, was low (20%) because azine formation was a major competing reaction under these low-temperature conditions. The absolute configuration of **13** was determined to be (*R*) by comparison of its optical rotation to the literature values.[22]



(12)

To explore further the selectivity between primary and tertiary C−H bonds, the reaction of **3a** with 2,3-dimethylbutane was examined. Under refluxing conditions (58 °C), using 1% of catalyst, this reaction resulted in the formation of the tertiary C−H insertion product **14** in 24% yield and 46% ee. The low yield in this reaction is probably due to the steric difficulty in reaction of the carbenoid at the tertiary C−H bond in 2,3-dimethylbutane, which is relatively crowded. Even though the phenyldiazoacetate was added dropwise over 1 h, carbene dimer **15** and azine **16** were formed (64:36 ratio) as major side products.

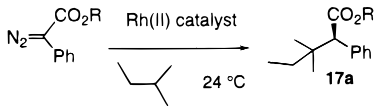


(13)

mole equiv. of Rh(II)	yield of **14**, %	ee of **14**, %	ratio **15**:**16**
0.002	4	13	32:68
0.01	24	46	64:36
0.05	27	66	75:25

As it is generally considered that the formation of both carbene dimer and azine is due to the reaction of the carbenoid with excess diazo compound,[23] a study was undertaken to try to improve the reaction by altering the amount of catalyst that was used. When 5% of catalyst was used, the yield of **14** remained about the same but the enantioselectivity was improved to 66% ee. Curiously, the ratio of **15** and **16** also changed (75:25). An even more dramatic change occurred when 0.2% of catalyst was used. Only a 4% yield of **14** in 13% ee was obtained, while the ratio of **15** to **16** was changed to 32:68. The observation that **15** is preferentially formed with high catalyst loading while **16** is formed with low catalyst loading is not consistent with the general view that both carbene dimer and azine are derived from reaction of a carbenoid with the diazo compound.[23] Instead, a more reasonable explanation is that only the azine **16** is formed from reaction of the carbenoid with the aryldiazoacetate, while the dimer **15** is formed by reaction between two rhodium carbenoid intermediates.

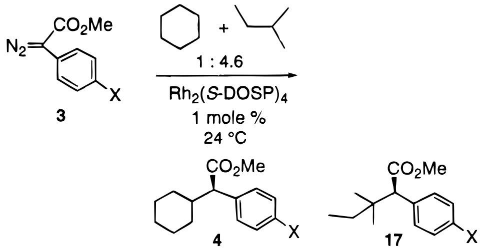
To explore the reactivity profile between secondary and tertiary sites, the reaction between **3a** and 2-methylbutane was examined. Decomposition of **3a** with Rh_2(*S*-DOSP)$_4$ at 24 °C in 2-methylbutane resulted in the formation of **17a** in 60% yield and 68% ee. The higher yield obtained with 2-methybutane compared to 2,3-dimethylbutane is presumably because the tertiary C−H bond in 2-methybutane is less sterically encumbered than the tertiary C−H bonds in 2,3-dimethylbutane. No evidence (<5%) for C−H insertion into the secondary C−H bond was observed. The regiochemistry is very different from the published results on the rhodium-catalyzed reaction of ethyl diazoacetate with 2-methylbutane, where a mixture of primary, secondary, and tertiary C−H insertion products were formed.[9d] We have previously communicated that Rh_2(*S*-DOSP)$_4$ appears to be ideally suited for C−H insertions of aryl- and vinyldiazoacetates.[19,24] Further confirmation of the remarkable attributes of Rh_2(*S*-DOSP)$_4$ was observed by evaluating a series of catalysts in the reaction of **3a** with 2-methylbutane. None of the traditional catalysts that were examined gave greater than 30% yield of C−H insertion product **17a**. Electron-rich catalysts are not particularly effective at intermolecular C−H insertion into alkanes,[9d] while of all the standard catalysts, only Rh_2(*S*-DOSP)$_4$ is fully soluble in 2-methylbutane under ambient conditions.



(14)

catalyst	yield, %	ee, %
Rh_2(*S*-DOSP)$_4$	60	68
$Rh_2(OOct)_4$	6	–
$Rh_2(OPiv)_4$	24	–
$Rh_2(TFA)_4$	19	–
$Rh_2(O_2CCPh_3)_4$	23	–
Rh_2(*R*-MEPY)$_4$	0	–

The lack of C−H insertion into the methylene group of 2-methylbutane is indicative of a steric influence because the reaction with cyclohexane demonstrates that secondary sites are susceptible to the C−H insertion. To compare the rate of reaction between secondary and tertiary sites, competition experiments were carried out using a mixture of cyclohexane and 2-methylbutane. Reaction of phenyldiazoacetate **3a** at 24 °C with a 1:4.6 mixture of cyclohexane and 2-methylbutane gave a 3.2:1 mixture of **4a** and **17a**. After considering the statistical factor, the tertiary C−H bond in 2-methylbutane is of similar reactivity to the C−H bond in cyclohexane. The same reaction with 4-bromphenyldiazoacetate **3b** gave a 2.6:1 mixture of **4b** and **17b**. The more electrophilic carbenoid that would be derived from **4b** appears to be more selective for a tertiary C−H bond than the carbenoid derived from **4a**.



(15)

	X	**4** : **17** ratio
a	H	76 : 24
b	Br	72 : 28

The absence of reactivity at the secondary C−H site in 2-methylbutane is a promising indication that chemoselectivity between secondary C−H bonds in different steric environments should be feasible. This concept was tested in the reaction of aryldiazoacetates with 2-methylpentane. Rh_2(*S*-DOSP)$_4$ catalyzed decomposition of **3a** in the presence of 2-methylpentane

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(22) Bright, D. A.; Mathisen, D. E.; Zieger, H. E. *J. Org. Chem.* **1982**, *47*, 3521.

(23) For a general discussion of carbene dimerization, see ref 6, pp 624−627.

(24) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233.

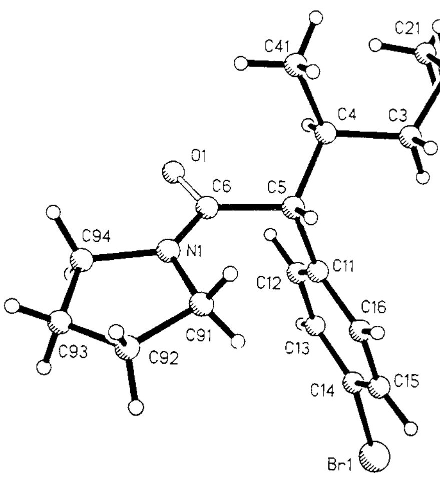
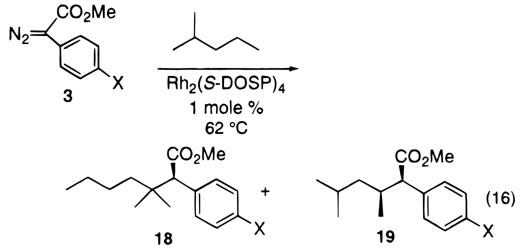


Figure 2. Absolute configuration of **20**.

under refluxing conditions (62 °C) gave rise to the tertiary C−H insertion product **18a** and the secondary C−H insertion product **19a** in a 58:42 ratio and 75% combined yield. Remarkably, **19a** was formed in a 4:1 diastereomeric ratio and 86% ee, while no evidence (<5%) of the regioisomeric secondary C−H insertion product was observed in the ^{1}H NMR of the crude mixture. A similar reaction with the bromophenyldiazoacetate **3b** gave a 77:23 ratio of **18b** and **19b** in 50% yield. The secondary C−H insertion product **19b** was again formed in a 4:1 diastereomeric ratio and 86% ee. The change in ratio is once again indicative that the more electrophilic carbenoid that would be derived from **3b** is more selective for a tertiary C−H site than the carbenoid derived from **3a**. The absolute configuration of **19b** was determined to be (2*R*,3*S*) by X-ray crystallographic analysis of the pyrrolidine amide derivative **20** of **19b** as shown in Figure 2.



(16)

	X	yield, % (18 + 19)	18: 19 ratio	ee of 18, %	de of 19, %	ee of 19, %
a	H	75	58 : 42	26	60	86
b	Br	50	77 : 23	33	60	86

On the basis of the reactivity profile described above, 2,2-dimethylbutane was considered to be a promising inert solvent for the C−H insertion chemistry because it has a reasonable boiling point and the C−H bonds in 2,2-dimethylbutane are at either primary or sterically crowded secondary sites. A test reaction with 2,2-dimethylbutane under the standard reaction conditions revealed that no appreciable reaction between the carbenoid and 2,2-dimethylbutane had occurred. This meant that 2,2-dimethylbutane is an appropriate inert solvent for reactions in which solid hydrocarbons such as adamantane are used as substrates. Reaction of **3a** with 2 equiv of adamantane in 2,2-dimethylbutane gave rise to 67% yield of the tertiary C−H insertion product **21a** in 90% ee. Similarly, the reaction between adamantane and **3b** gave a 70% yield of **21b** in 96% ee.

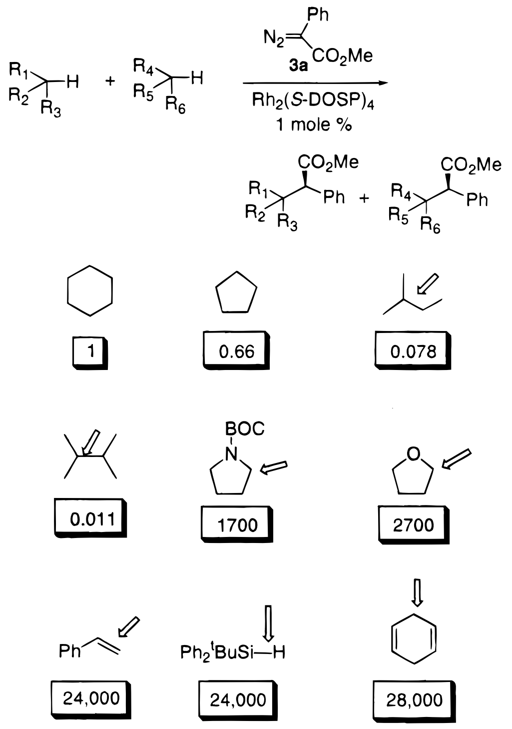
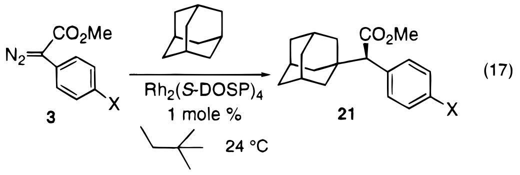


Figure 3. Relative rates of reaction of **3a** with various substrates.



(17)

	X	yield, %	ee, %
a	H	67	90
b	Br	70	96

The absolute configuration of **4a**, **10a**, **13**, and **19b** was determined unequivocally. The absolute configuration of all the other products is tentatively assigned on the assumption that the *re* face of the rhodium carbenoid is attacked in each case. Supporting evidence for this tentative stereochemical assignment was obtained from the CD spectra of **4a**, **5a**, **13**, **14**, **17a**, **18a**, **18b**, **19a**, **19b**, **21a**, and **21b**, all of which show a strongly negative absorption at 220 nm.[21]

One of the most distinctive features of the C−H insertion chemistry of aryldiazoacetates is the remarkable chemoselectivity that is possible. To quantify this effect competition experiments between various substrates were examined and the results are summarized in Figure 3. In most instances the competition experiments were run using a 1:1 mixture of substrates, but in the cases where one of the substrates was considerably more reactive that the other, the ratio of substrates was altered accordingly. From these data, it is clear that these C−H insertions display remarkable regioselectivity. Reaction with THF and *N*-BOC-pyrrolidine is more favorable than reaction with cyclohexane by factors of 1700 and 2400, respectively. C−H activation of THF is about 10 times less favorable than Si−H insertion or cyclopropanation of styrene.

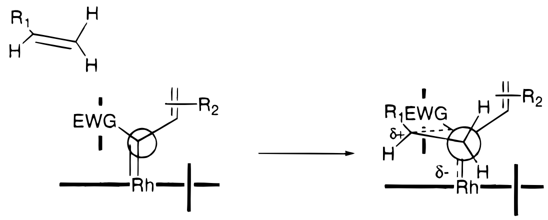


Figure 4. Model for asymmetric cyclopropanation.

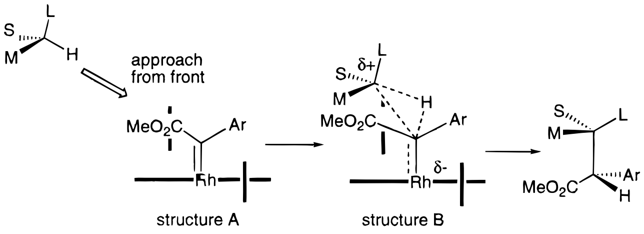


Figure 5. Model for the asymmetric C−H insertion.

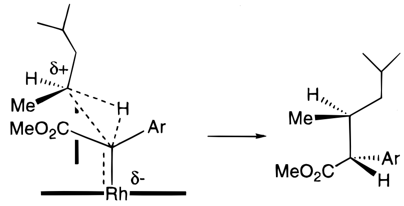
Even though selective reactions at tertiary C−H sites are possible, in general there is a delicate balance in reaction between secondary and tertiary C−H sites. Tertiary sites are preferred on electronic grounds but secondary sites are preferred on steric grounds.

Discussion

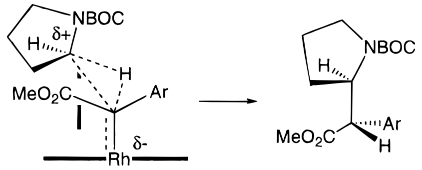
From the above experiments it is apparent that the asymmetric C−H insertion of aryldiazoacetates has many similarities to the asymmetric cyclopropanation of phenyl- and vinyldiazoacetates. The most reactive C−H bonds are those in which the carbon would be able to stabilize a buildup of positive charge during the transition state, although the rhodium carbenoid is a sterically demanding reagent and steric effects may dominate over electronic effects. In both reactions the influence of ester size and solvent on the asymmetric induction follows a parallel trend. We have proposed that the asymmetric cyclopropanation occur by a transition state presented in Figure 4.[15] The catalyst behaves as if it is D_2 symmetric with the arylsulfonyl groups aligned $\alpha,\beta,\alpha,\beta$. The two thickened vertical lines in Figure 4 represent the blocking effects of the arylsulfonyl groups (due to the symmetry of the catalysts, the chiral influence on the bottom face of the catalysts would be the same as the top face). The cyclopropanation is considered to be concerted but nonsynchronous with the alkene approaching in a side-on mode over the ester group of the carbenoid.[15] Apparently, the major reason for the success of the phenyl and vinyldiazoacetate cyclopropanations is that the trajectory of approach of the alkene to the carbenoid is much more demanding than is the case with other carbenoid systems.

The generally accepted mechanism for intramolecular C−H insertions involves the direct insertion between the carbenoid and the C−H bond by means of a three-membered transition state.[25] Due to the similar trends between the cyclopropanation and the C−H insertion of aryldiazoacetates, we propose that the C−H insertion also occurs in a concerted but nonsynchronous manner with build up of positive charge at the carbon of the C−H bond (Figure 5). The kinetic isotope effect that was observed for cyclohexane and tetrahydrofuran is consistent with such a mechanistic interpretation. The higher value obtained with THF is indicative that the transition state for cleavage of the C−H bond is more advanced in THF C−H insertions than the cyclohexane C−H insertions. The selectivity toward tertiary C−H sites and for the 2-position of tetrahydrofuran is consistent with this mechanism because these are the sites that are best suited to stabilize the positive charge buildup in the transition state. The actual trajectory of approach of the alkane is not known, but to generate the correct absolute stereochemistry, the alkane would need to approach over the ester group of the carbenoid. The increased reactivity of bromophenyldiazoacetate **3b** compared to phenyldiazoacetate **3a** for reaction at a tertiary C−H site rather than a secondary C−H site is also consistent with this model, because charge build up in the transition state of **3b** would be enhanced over **3a**. The generally higher enantioselectivity of C−H insertions at secondary sites compared to tertiary sites would presumably be because a close approach of the alkane to the catalyst is less likely for reaction at a crowded tertiary C−H insertion site compared to a secondary site.

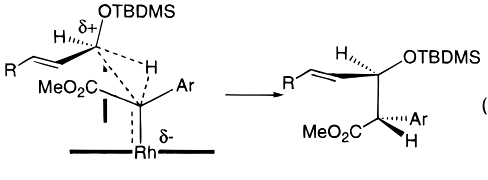
When the C−H insertion occurs at a pro-chiral methylene group, two stereogenic centers are generated during the C−H insertion. Although a full understanding of the structural requirements for the diastereoselection is not yet available, it is clear that impressive diastereocontrol is possible in certain systems.[18,19] The diastereocontrol that is observed is consistent with the model shown in Figure 5 where the large group (L) projects upward from the catalyst, the small group (S) points toward the carbenoid and slightly toward the catalyst, and the medium group (M) projects away from the carbenoid but slightly toward the catalyst. Using this model, the reaction with 2-methypentane would be predicted to form the (2*R*,3*S*) isomer (eq 18), the reaction with *N*-BOC-pyrrolidine would be predicted to form the (2*S*,2′*S*) isomer (eq 19), while the reaction with allyl silyl ethers would be expected to form the (2*S*,3*R*) products (eq 20). Further studies will need to be carried out to determine if this simple predictive model is generally applicable.



(18)



(19)



(20)

One of the intriguing discoveries that was made during these studies is that in the case of phenyldiazoacetate **3a**, when poor trapping agents are present, carbene dimer formation is preferred using high catalyst loading while azine formation is preferred using low catalyst loading. This result is an indication that the carbene dimer from **3a** is likely formed by reaction between two rhodium carbenoid species, and this suggestion is counter to the generally held opinion that carbene dimers arise from reaction of a carbenoid with the diazo compound.[23] Furthermore,

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[25] For a general discussion on the proposed mechanisms of intramolecular C−H insertions, see ref 6, pp 133−162.

these observations indicate that the rhodium carbenoid has a sufficiently long lifetime in the hydrocarbon solvents to allow two rhodium carbenoids to react together. Further studies are in progress to determine the full ramifications of this observation.

In summary, these studies demonstrate that carbenoids derived from aryldiazoacetates are capable of effective asymmetric C−H activation of a range of alkanes and tetrahydrofuran. These carbenoids are considerably more chemoselective than carbenoids derived from diazoacetates and strongly favor C−H insertions at secondary and tertiary sites. Even though general reviews on C−H activation of hydrocarbons[1,2a,b,3] have largely ignored carbenoid C−H insertions, it is clear from this work that rhodium carbenoids derived from aryldiazoacetates are practical intermediates for asymmetric intermolecular C−H activation. Due to the high regioselectivity, diastereoselectivity, and enantioselectivity of these reactions, we expect this chemistry to be of considerable value in organic synthesis.

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Supporting Information Available: Complete experimental data, X-ray data for **11** and **20**, and NMR data for **3l**, **4b**, **4e**, **4g**, **4h**, **4i**, **4j**, **8**, **10k**, **11**, **13**, **14**, **17a**, **17b**, **18a**, **18b**, **19a**, **19b**, **20**, **21a** and **21b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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