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Catalytic asymmetric C–H activation by methyl thiophen-3-yldiazoacetate applied to the synthesis of (+)-cetiedil

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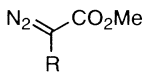
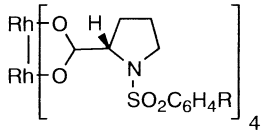
Abstract—Dirhodium tetraprolinate catalyzed reaction of methyl thiophen-3-yldiazoacetate results in intermolecular allylic C–H activation by means of rhodium carbenoid induced C–H insertion. The reaction with 1,4-cyclohexadiene was applied to the asymmetric synthesis of (+)-cetiedil. © 2002 Elsevier Science Ltd. All rights reserved.

Intermolecular C–H activation by means of a rhodium carbenoid induced C–H insertion offers attractive new synthetic strategies for the preparation of complex molecules.[1] The original studies of C–H insertions with carbenoids derived from diazoacetates, diazoketones and diazoacetoacetates demonstrated that such reactions were feasible but were only generally useful when the reactions were carried out intramolecularly.[2] The main difficulties associated with these carbenoids were their tendency to undergo dimerization and their limited chemoselectivity in intermolecular C–H insertions.[2] Recently, it has been demonstrated that rhodium carbenoids derived from diazo compounds functionalized with both donor and acceptor groups (**1**) are capable of undergoing highly efficient intermolecular C–H insertions.[3] When these reactions are catalyzed by $Rh_2(S\text{-DOSP})_4$ (**2**) high asymmetric induction can be achieved.[4–8] The potential of this chemistry as a new strategic approach for synthesis has been illustrated by examples where the C–H activation is a surrogate of some of the classic reactions of organic synthesis, such as the Claisen rearrangement,[5] the Michael reaction,[6] the Mannich reaction[7] and the aldol reaction.[8]



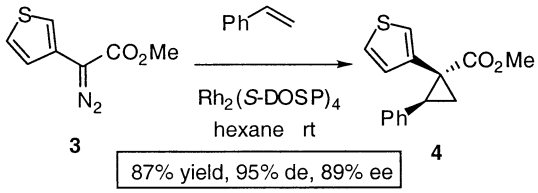
1a: R = vinyl
1b: R = aryl



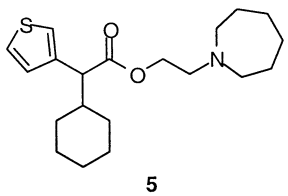
R = $C_{12}H_{25}$ [$Rh_2(S\text{-DOSP})_4$]

2

A critical requirement for the successful outcome of these asymmetric intermolecular C–H insertions is the presence of a donor substituent on the carbenoid.[1] Consequently, the vast majority of the published examples[1,4–8] have been conducted with substituted phenyldiazoacetates. In order for this chemistry to become broadly useful, it will be necessary to expand the range of functionality that can act as the donor group. As an extension to the use of vinyl (**1a**) and substituted phenyl (**1b**) as donor groups, we recently reported the use of heteroaryldiazoacetates in asymmetric cyclopropanation.[9] An illustrative example is the $Rh_2(S\text{-DOSP})_4$-catalyzed cyclopropanation of methyl thiophen-3-yldiazoacetate **3** to form cyclopropane **4**, in 87% yield, 95% de and 89% ee (Eq. (1)).[9] In this paper we describe our exploratory studies to determine if **3** will undergo C–H activation chemistry and to illustrate the utility of this chemistry by a short asymmetric synthesis of (+)-cetiedil **5**.[10] Cetiedil is an effective K^+ channel blocker,[11] possesses several therapeutic activi-



(1)



5

Keywords: C–H activation; rhodium carbene; C–H insertion; diazo compounds.

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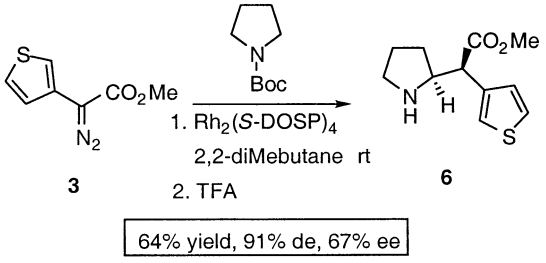
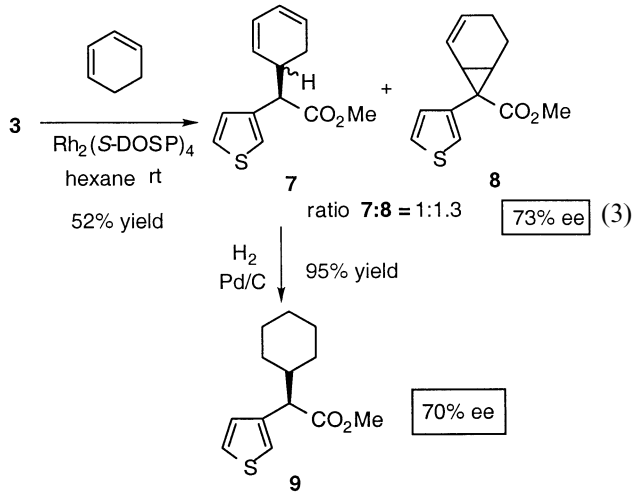
ties,[12] and is a potent blocker of acetylcholine and choline fluxes.[13] The reported synthesis of the pure enantiomers of **5** required resolution by fractional crystallization of a chiral precursor to **5**.[10]

The major challenge in extending the reaction of **3** from cyclopropanation chemistry to C–H activation chemistry is to ensure effective trapping of the carbenoid. The initial studies with cyclohexane were not promising. $Rh_2(S\text{-DOSP})_4$-catalyzed reaction of **3** in cyclohexane as solvent gave no C–H insertion product, even under reflux conditions, which usually enhances the C–H activation chemistry.[4] Only carbene dimerization was observed. In order to improve the chances of an intermolecular C–H insertion, the reaction of **3** with *N*-Boc-pyrrolidine was examined because *N*-Boc-pyrrolidine has been shown to be 2000 times more reactive towards C–H insertion than cyclohexane.[4] In this case the C–H insertion product **6** was effectively formed in 64% yield with 91% de and 67% ee (Eq. (2)). This result compares favorably with the parallel reaction reported for methyl phenyldiazoacetate.[7a] The absolute stereochemistry of **6** has not been determined but it is predicted to be (2*S*,2″*S*) in analogy to the reaction with methyl phenyldiazoacetate.[7a]



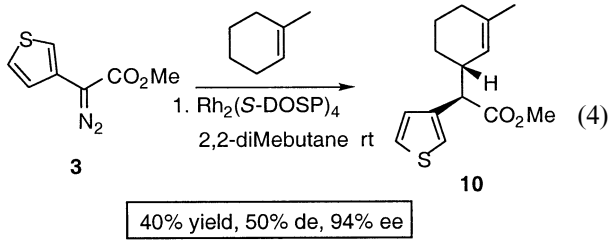
(2)

C–H Insertion was also possible at other activated positions. The reaction of **3** with 1,3-cyclohexadiene resulted in the formation of C–H insertion product **7** and cyclopropanation product **8** in a combined yield of 52% (Eq. (3)). The C–H insertion product **7** was formed as an inseparable mixture of diastereomers, and so in order to determine the extent of asymmetric induction, **7** was reduced to the cyclohexane **9** which was formed in 70% ee. The absolute stereochemistry of **7** is predicted to be *R* in analogy to the product derived from the reaction with methyl phenyldiazoacetate.[5a] The cyclopropanation product **8** was formed in 73% ee.



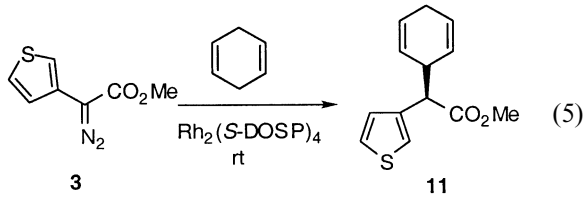
(3)

One of the most notable features of the C–H activation chemistry of donor–acceptor substituted rhodium carbenoids is that they are often highly regioselective.[1,4–8] In order to explore whether the carbenoid from **3** has similar characteristics, the $Rh_2(S\text{-DOSP})_4$ catalyzed reaction of **3** with 1-methyl-1-cyclohexene was examined (Eq. (4)). A high level of regioselectivity was observed as C–H insertion occurred only at the least crowded allylic methylene site. The C–H insertion product **10** was formed in 40% yield, 50% de and 94% ee.



(4)

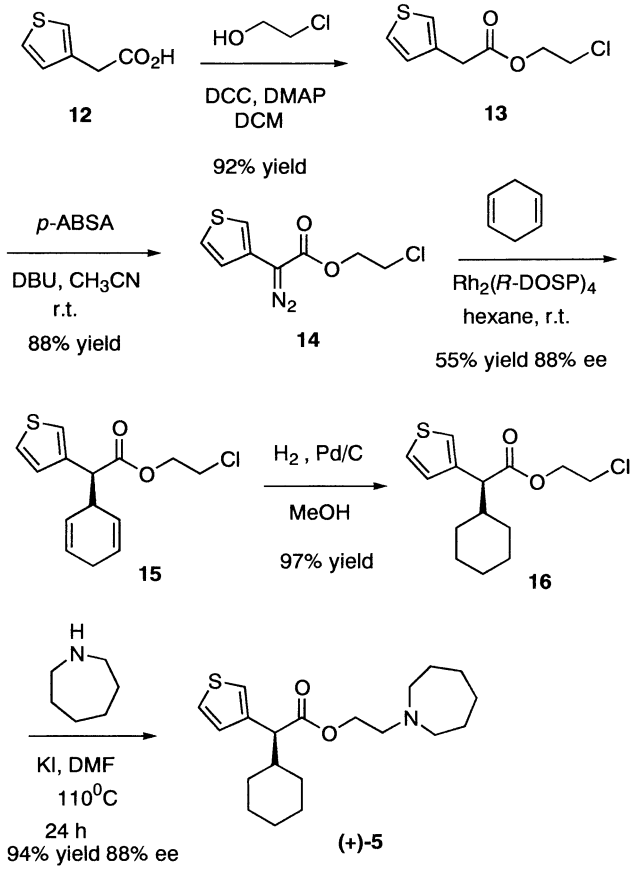
A more efficient C–H insertion was achieved on reaction of **3** with 1,4-cyclohexadiene. As is typical of $Rh_2(S\text{-DOSP})_4$-catalyzed reactions,[14] the highest enantioselectivity was obtained when the reaction was carried out in hydrocarbon solvent. The C–H insertion product **11** was formed in 65% ee when dichloromethane was used as solvent and in 88% ee when hexane was used as solvent.



(5)

solvent	yield, %	ee, %
hexane	57	88
CH_2Cl_2	55	65

A practical utility of this heteroaryldiazoacetate intermolecular C–H insertion was envisioned in the asymmetric synthesis of (+)-cetiedil **5**. Even though the direct C–H activation of cyclohexane with thiophen-3-yldiazoacetates is not feasible, the reaction of thiophen-3-yldiazoacetates with cyclohexadienes followed by reduction would be a rapid asymmetric entry into the cetiedil core. In order to limit the number of synthetic steps after the C–H activation step, the reaction was conducted on the 2-chloroethyl ester derivative (Scheme 1). Diazoacetate **14** was synthesized by standard esterification of the commercially available acid **12** to **13** (92% yield), followed by diazo transfer using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA)[15] and DBU (88% yield). C–H insertion of 1,4-cyclohexadiene with diazoacetate **14** catalyzed by $Rh_2(R\text{-DOSP})_4$ formed the



Scheme 1.

precursor (+)-**15** (55% yield and 88% ee). Catalytic hydrogenation (97% yield) followed by introduction of the hexamethyleneimine functionality furnished (+)-cetiedil **5** in 94% yield with 88% ee.[16]

In summary, the intermolecular C–H activation chemistry of methyl thiophen-3-yldiazoacetate **3** is not as general as that reported for substituted phenyldiazoacetates. However, C–H activation by means of C–H insertion can be carried out at allylic positions and α to nitrogen. The synthetic potential of this chemistry was illustrated by a short asymmetric synthesis of (+)-cetiedil.

Supplementary material. Detailed experimental conditions for the synthesis of compounds **3**–**16**.

Acknowledgements

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16. In analogy to **9**, the absolute stereochemistry of (+)-**5** is predicted to be *S*.