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Enantioselective *cis*-β-lactam synthesis by intramolecular C–H functionalization from enoldiazoacetamides and derivative donor–acceptor cyclopropenes†

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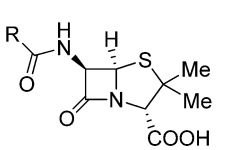
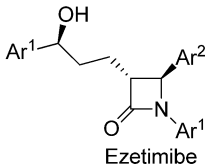
β-Lactam derivatives are produced through intermediate donor–acceptor cyclopropene intermediates in high yield, exclusive *cis*-diastereoselectivity, and high enantiocontrol in a chiral dirhodium carboxylate catalyzed intramolecular C–H functionalization reaction of enoldiazoacetamides.

Introduction

The importance of β-lactam compounds (2-azetidinones) in biology and medicine is undisputed since the discovery of the antibiotic activity of the bicyclic penicillin in 1928,[1,2] and monocyclic β-lactams that include the plasma cholesterol-lowering Ezetimibe[3] also show biological activity.[4] Considerable effort has been focused on chemical catalysis for the construction of β-lactams, including those through catalytic intramolecular amide N–H insertion reactions of diazo compounds,[5] and asymmetric synthesis has been a primary focus.[2,6] However, the same C–H functionalization methodology of diazo compounds that has provided exceptional selectivities in intermolecular reactions[7] and intramolecular syntheses of γ-lactones and γ-lactams[8] has been limited in efforts to synthesize β-lactams.



Penicillin core srtucture

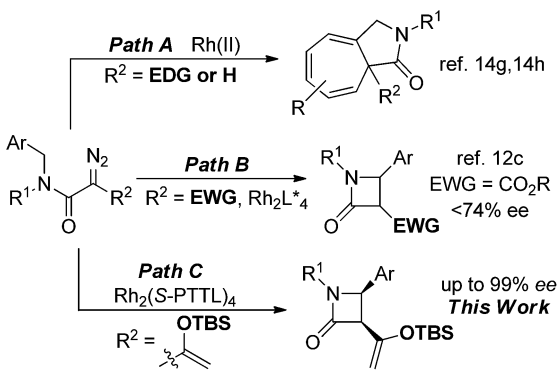


Ezetimibe

Ar^1 = 4-FC_6H_4, Ar^2 = 4-HOC_6H_4

Direct intramolecular C–H functionalization of diazoacetamides catalyzed by transition metal catalysts is straightforward.[9] The amide nitrogen activates the adjacent C–H bond for insertion. Although β-lactam formation by photocatalysis was described fifty years ago,[10] and the first enantioselective process was reported in 1992,[2c,11] there have only been a few examples that have overcome a majority of the electronic, steric, and conformational factors which control the selectivity of this process.[12,13] Competing reactions include intramolecular cycloaddition to an aromatic ring of an aryl- or heterocycle attachment (Buchner reaction), addition to a carbon–carbon multiple bond of an allylic or propargylic system, or regioselective formation of a γ-lactam from C–H functionalization.[14] Product selectivity is highly dependent on the diazo compound that is employed;[12,14] for example, acceptor or donor–acceptor diazoamides form aromatic cycloaddition products when catalyzed by dirhodium catalysts (Scheme 1, Path A, R^2 = H or EDG), but acceptor–acceptor diazoamides produce β-lactam products by a C–H functionalization reaction (Path B, R^2 = EWG).

To achieve high selectivity in C–H functionalization reactions that form β-lactam products, acceptor–acceptor diazoamides (R^2 = EWG) have been constructed to avoid side



Scheme 1 Diazoacetamide substrate dependence on chemoselectivity.

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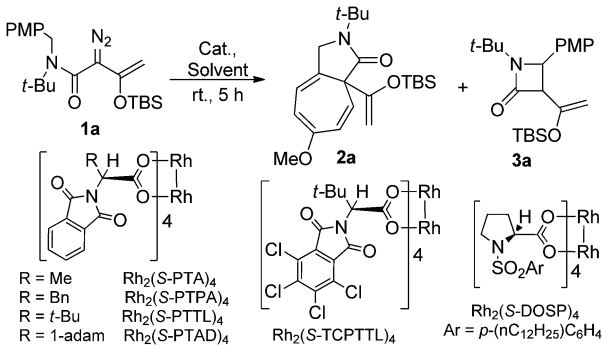
reactions, but high regio- and enantiocontrol (>90% ee) has only been demonstrated in constrained cyclic systems in which the aliphatic γ-position has been made inaccessible for insertion.[12a,b] We have developed enoldiazoacetates as a new class of stable donor–acceptor diazo compounds with extensive applications for cycloaddition reactions.[15] An attractive feature of this vinyldiazo compound in catalytic reactions with dirhodium(II) carboxylates is the apparent donor–acceptor cyclopropene intermediate that serves as a resting state for the apparent reactive metal carbene intermediate.[16] Could enoldiazoacetamides form intermediate donor–acceptor cyclopropenes and be precursors to donor–acceptor metal carbene intermediates on the pathway to C–H functionalization? Earlier work by Müller suggested that enantioselectivity in cyclopropanation reactions of styrene with an enoldiazoacetate is significantly greater than that with the corresponding diazoacetoacetate.[17] We wish to report that asymmetric catalysis with donor–acceptor *N*-benzyldiazoamides proceeds through donor–acceptor cyclopropene intermediates to form *cis*-disubstituted β-lactams by intramolecular C–H functionalization in high yields and stereoselectivities (Path C).

Results and discussion

In initial studies we selected the *N*-*tert*-butyl-*N*-(*p*-methoxybenzyl)enoldiazoacetamide **1a** as a model substrate since previous studies have shown that the *tert*-butyl group fixed the reactant in the conformation in which the benzyl and diazo functional groups are *syn* to each other.[13] In this conformation C–H insertion into the *tert*-butyl group is prevented, but aromatic cycloaddition into the anisyl group could be competitive with C–H insertion into its benzyl group, and indeed this competition was observed (Table 1). The Buchner product **2a** was dominant in reactions catalyzed by sterically unencumbered $Rh_2(OAc)_4$ or the electrophilic $Rh_2(pfb)_4$, but with the sterically restrictive $Rh_2(tpa)_4$ or $Rh_2(esp)_2$ the sole product was

Table 1 Optimization of reaction conditions for the enantioselective C–H functionalization of enlodiazoacetamide **1a**[a]

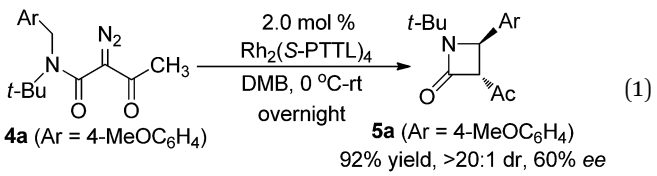


Entry	Rh(II)	Solvent	**2a** : **3a**[e]	Yield[f], (%) **2a** + **3a**	ee[g] (%) **2a**/**3a**
1[b]	$Rh_2(OAc)_4$	$DCCl_3$	80 : 20	87	—/—
2[b]	$Rh_2(pfb)_4$	$DCCl_3$	80 : 20	89	—/—
3[b]	$Rh_2(tpa)_4$	$DCCl_3$	<5 : 95	92	—/—
4[b]	$Rh_2(esp)_2$	$DCCl_3$	<5 : 95	87	—/—
5[b]	Rh_2(*S*-DOSP)$_4$	$DCCl_3$	37 : 63	90	27/10
6[b]	Rh_2(*S*-PTA)$_4$	$DCCl_3$	25 : 75	92	35/30
7[b]	Rh_2(*S*-PTPA)$_4$	$DCCl_3$	33 : 67	90	53/41
8[b]	Rh_2(*S*-PTTL)$_4$	$DCCl_3$	<5 : 95	93	—/64
9[b]	Rh_2(*S*-PTAD)$_4$	$DCCl_3$	<5 : 95	93	—/64
10	Rh_2(*S*-PTTL)$_4$	DCM	<5 : 95	89	—/65
11	Rh_2(*S*-PTTL)$_4$	DCE	<5 : 95	88	—/68
12	Rh_2(*S*-PTTL)$_4$	Toluene	<5 : 95	76	—/75
13	Rh_2(*S*-PTTL)$_4$	CF_3Ph	<5 : 95	72	—/67
14	Rh_2(*S*-PTTL)$_4$	Cyclohexane	<5 : 95	90	—/82
15	Rh_2(*S*-PTTL)$_4$	TBME	<5 : 95	91	—/71
16	Rh_2(*S*-PTTL)$_4$	DMB	<5 : 95	83	—/88
17[c]	Rh_2(*S*-PTTL)$_4$	DMB	<5 : 95	85	—/92
18[d]	Rh_2(*S*-PTTL)$_4$	DMB	<5 : 95	82	—/91
19[c]	Rh_2(*S*-TCPTTL)$_4$	DMB	<5 : 95	88	—/89

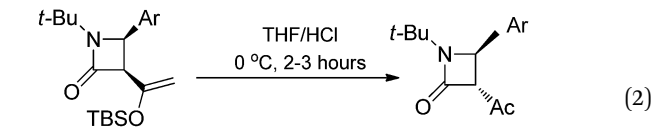
[a] Reactions were carried out at room temperature on a 0.2 mmol scale in 1.0 mL solvent with 2.0 mol% dirhodium catalyst in 5 hours. [b] Reactions were carried out at room temperature on a 0.2 mmol scale in 0.5 mL $DCCl_3$ with 2.0 mol% dirhodium catalyst in an NMR tube. [c] The reaction was carried out at 0 °C in 3 hours. [d] The reaction was carried out at −20 °C overnight. [e] The ratio was determined by integration of characteristic ^{1}H NMR absorptions from the spectrum of the reaction mixture. [f] Isolated yield after chromatography. [g] Enantioselectivity was determined by chiral HPLC analysis, see ESI for details. TBME = *tert*-butyl methyl ether; DMB = 2,2-dimethylbutane.

the *cis*-disubstituted β-lactam **3a**, formed by C–H insertion into the benzylic position. With asymmetric catalysts similar steric influences were operative so that increasing the steric bulk of the chiral Hashimoto dirhodium(II) carboxylate catalyst ligand increased the **3a**/**2a** ratio and, also, enhanced enantioselectivity (entries 5–9) for both products. Both Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-PTAD)$_4$ gave β-lactam **3a** as the only product in high yield with 64% ee (entries 8 and 9). We chose Rh_2(*S*-PTTL)$_4$ for further optimization and, after screening solvents and reaction temperatures, the reaction carried out at 0 °C in 2,2-dimethylbutane (DMB) gave the optimum result with 85% isolated yield and 92% ee of **3a** (entry 17).[18] The more Lewis acidic Rh_2(*S*-TCPTTL)$_4$ gave **3a** in higher yield but slightly lower % ee. Chiral dirhodium carboxamidates were not effective as catalysts for this transformation, but the more reactive Rh_2(*S*-DOSP)$_4$ produced a mixture of **2a** and **3a** with low enantioselectivities (entry 5).

The observed high enantioselectivity obtained from catalytic intramolecular C–H insertion of **1a** was not observed with the corresponding diazoacetamide. β-Lactam **5a** was obtained in only 60% ee for when diazoacetamide **4a** was reacted under the same conditions (eqn (1)) and, in contrast to the exclusive *cis*-selectivity observed in the formation of β-lactam **3a**, **5a** was formed with exclusive *trans*-selectivity.[19] The *trans* β-lactam product was also obtained in high yield in reactions catalyzed by achiral [$RuCl_2$(*p*-cymene)]$_2$ reported by Chi.[14f] The reason for this difference in diastereoselectivity is probably isomerization of the β-ketoamide and, indeed, *cis*-**3c** is converted to *trans*-**5c** upon hydrolysis (eqn (2)) without loss of enantioselectivity.



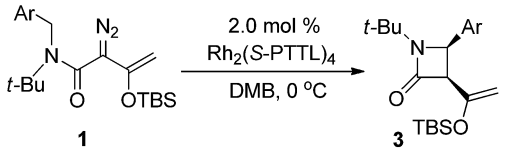
4a (Ar = 4-MeOC$_6$H$_4$) **5a** (Ar = 4-MeOC$_6$H$_4$)
92% yield, >20:1 dr, 60% *ee* (1)



3c (Ar = 4-ClC$_6$H$_4$) (3*S*,4*S*)-**5c** (Ar = 4-ClC$_6$H$_4$)
93% ee 77% yield, 93% *ee* (2)

The scope of the C–H functionalization reaction of representative diazoacetamides **1** was investigated with Rh_2(*S*-PTTL)$_4$ catalysis under the optimum conditions established for **1a** (Table 2). In all examples, *cis*-β-lactam **3** was generated exclusively and in high yield (80–92%) and with high enantioselectivities (83–99% ee). The % ee of β-lactam **3** was lower when strong electron-withdrawing substituents were on the aromatic ring, and these reactions also required longer times for completion than did enoldiazoacetamides with electron-donating substituents (entries 6 and 7). Lower enantioselectivities were obtained with substrates having *m*- or *o*-substituents, and the lowered % ee was independent of a second substituent at the *para* position (entries 10 and 11) or of the size of the *ortho* substituent (entries 12 and 13). Using the *N*,*N*-diisopropylamide instead of the benzyl-*t*-butylamide also resulted in a β-lactam with lower enantioselectivity but good yield. Rh_2(*S*-NTTL)$_4$ gave higher enantiocontrol by 7% ee in the reaction of unsubstituted enoldiazo acetamide **1b** (entry 2), but the same or lower enantioselectivities were observed in reactions with **1a**, **1f**, **1g**, and **1k**. Product mixtures were obtained when Ar = the heteroaryl 3-furanyl group and included products from [3 + 4]-cycloaddition.[7] It is noteworthy that β-lactam **3i** with the *p*-dimethylamino substituent was obtained with 99% ee in 80% yield

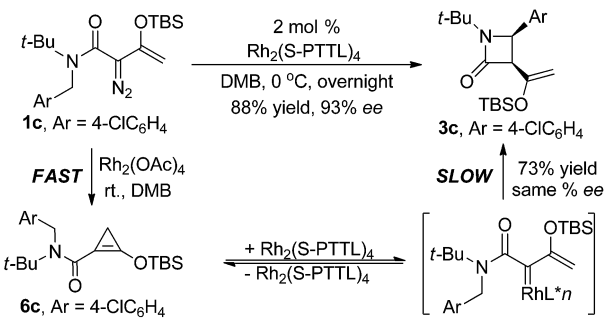
Table 2 Enantioselective C–H functionalization of **1**[a]



1 **3**

Entry	Ar (**1**)	*t* (hours)	**3**	Yield[c] (%)	ee[d] (%)
1	4-MeO$_6$H$_4$ (**1a**)	3	**3a**	85	92
2	C$_6$H$_5$(**1b**)	12	**3b**	82 (81)[b]	80 (87)[b]
3	4-ClC$_6$H$_4$ (**1c**)	5	**3c**	88	93
4	4-MeC$_6$H$_4$ (**1d**)	5	**3d**	92	93
5	4-FC$_6$H$_4$ (**1e**)	5	**3e**	88	91
6	4-BrC$_6$H$_4$ (**1f**)	12	**3f**	89	89
7	4-NO$_2$C$_6$H$_4$ (**1g**)	12	**3g**	88	83
8	4-PhC$_6$H$_4$ (**1h**)	5	**3h**	89	91
9	4-Me$_2$NC$_6$H$_4$ (**1i**)	5	**3i**	80	99
10	3,4-(MeO)$_2$C$_6$H$_3$ (**1j**)	5	**3j**	81	77
11	3-MeOC$_6$H$_4$ (**1k**)	5	**3k**	92	78
12	2-MeOC$_6$H$_4$ (**1l**)	12	**3l**	85	25
13	1-Naphthyl (**1m**)	5	**3m**	85	24
14[e]	*N*,*N*-Diisopropyl (**1n**)	5	**3n**	81	67
15[f]	4-ClC$_6$H$_4$ (**1c′**)	5	**3c′**	84	92

[a] Reactions were carried out on a 0.2 mmol scale in 1.0 mL DMB with 2.0 mol% Rh_2(*S*-PTTL)$_4$. [b] Results in parentheses was catalyzed by Rh_2(*S*-NTTL)$_4$. [c] Isolated yield. [d] Enantioselectivity was determined by chiral HPLC analysis, see ESI for details. [e] *N*,*N*-Diisopropyl instead of *N*-*tert*-butyl-*N*-benzyl diazoamide was used. [f] TIPS protection instead of TBS was used.

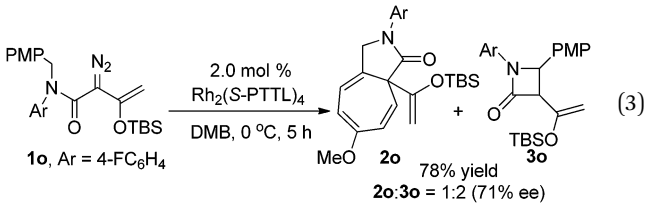


1c, Ar = 4-ClC$_6$H$_4$ **3c**, Ar = 4-ClC$_6$H$_4$

6c, Ar = 4-ClC$_6$H$_4$

Scheme 2 Donor–acceptor cyclopropenes are reaction intermediates in metal carbene formation.

(entry 9). And TIPS protected substrate **1c′** gave similar results as **1c** (entry 3 *vs.* entry 15). When an *N*-aryl substituent was used instead of the *t*-butyl group diazo compound **1o**, the reaction gave both Buchner reaction and C–H functionalization products in a 1 : 2 ratio with 78% total yield, and β-lactam **3o** was formed with 71% ee (eqn (3)).

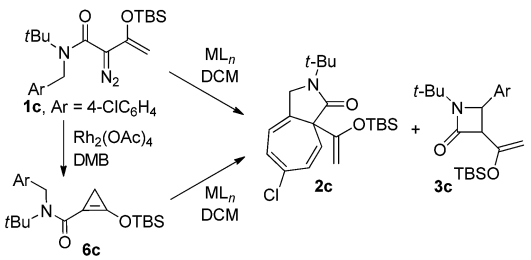


(3)

As is suggested by the reaction conditions, these reactions are relatively rapid. However, close spectroscopic inspection of reactions with **1c** revealed that donor–acceptor cyclopropene **6c** was formed at a much faster rate than was the product from C–H insertion. To determine if the donor–acceptor cyclopropene is a precursor to the donor–acceptor chiral metal carbene intermediate whose intramolecular C–H insertion produces highly enantiomerically enriched β-lactam, reaction of **1c** was performed in DMB with 2.0 mol% $Rh_2(OAc)_4$ and at 5 min was filtered through Celite to remove the $Rh_2(OAc)_4$. Spectral analysis of the residue showed <1% **1c**, 8 ± 1% **3c**, and 92 ± 2% donor–acceptor cyclopropene **6c**. This mixture was then submitted to the same reaction conditions as reported in Table 2 with Rh_2(*S*-PTTL)$_4$ catalysis to produce **3c** in 73% isolated yield and 83 ± 3% ee. Subtracting racemic product formed from $Rh_2(OAc)_4$ gives **3c** formed from donor–acceptor cyclopropene **6c** with the same selectivity as that formed from **1c** (Scheme 2).

That donor–acceptor cyclopropene **6** can serve as a precursor to an intermediate metal carbene of dirhodium(II) which undergoes C–H insertion prompted us to investigate if other transition metals, particularly those of copper(I) and silver(I), could undergo the same transformation. Although both of these catalytically active metal ions are known to form metal carbenes directly from diazo compounds,[7,8,20] they undergo Lewis acid catalyzed reactions with enoldiazoacetates,[15] and they are distinctly different from dirhodium(II) carboxylates in cycloaddition reactions with nitrones.[18c] Since C–H insertion is notably unique to metal carbenes, reactions of metal catalysts with enoldiazoacetamides or their derivative cyclopropenes would be a demonstration of metal carbene involvement with these catalysts. To undertake this investigation, reactions were performed on both enoldiazoacetamide **1c** and cyclopropene **6c** that was prepared from **1c** by treatment with $Rh_2(OAc)_4$ in DMB as previously described, and these results are described in Table 3. The copper(I) and silver(I) catalysts are distinctly different from each other and from $Rh_2(OAc)_4$ in their reactions with enoldiazoacetamide **1c**: aromatic cycloaddition is favored over C–H-insertion in reactions of **1c** in the catalyst order: $Ag(SbF_6)$ > $Cu(MeCN)_4PF_6$ > $Rh_2(OAc)_4$ (entries 1 and 2); and this difference is also reflected in the results from reactions with cyclopropene **6c**. Surprisingly, the $Cu(MeCN)_4PF_6$ and $AgSbF_6$ catalyzed reactions with enoldiazoacetamide **1c** provide more of the

Table 3 Comparison of catalysts in C–H insertion and aromatic cycloaddition reactions of **1c** and **6c**[a]



Entry	Catalyst	Reactant	*t* (hours)	**2c** : **3c**	Yield[d] (%) **2c** + **3c**	ee[e] (%) **3c**
1[b]	$AgSbF_6$	**1c**	12	>95 : 5	87	—
2[b]	$Cu(MeCN)_4PF_6$	**1c**	12	85 : 15	85	—
3[c]	$Cu(MeCN)_4PF_6$/(*S*)-*t*-BuBox	**1c**	48	<5 : 95	10	28
4[b]	$Cu(MeCN)_4PF_6$	**6c**	12	75 : 25	87	—
5[c]	$Cu(MeCN)_4PF_6$/(*S*)-*t*-BuBox	**6c**	12	<5 : 95	89	30
6[b]	$AgSbF_6$	**6c**	12	85 : 15	82	—
7[c]	$AgSbF_6$/(*S*)-*t*-BuBox	**6c**	12	75 : 25	91	24
8	$Sc(OTf)_3$	**6c**	12	—	NR[f]	—
9	$La(OTf)_3$	**6c**	12	—	NR[f]	—
10	$BF_3 \cdot Et_2O$	**6c**	12	—	NR[f]	—
11[g]	(—)	**6c**	12	—	NR[f]	—

[a] Reactions were carried out on a 0.2 mmol scale in 1.0 mL DCM. [b] Reactions were carried out with 10 mol% Lewis acid catalyst. [c] Reactions were carried out with 10 mol% Lewis acid catalyst and 12 mol% ligand. [d] Isolated yield. [e] The enantioselectivity was determined by chiral HPLC analysis, see ESI for details. [f] Neither **2c** nor **3c** was observed, and only slowly decomposition of **6c** was observed. [g] The reaction was carried out in 70 °C.

aromatic cycloaddition product, which is reported to be due to a more electrophilic metal carbene intermediate,[13] than do their reactions with donor–acceptor cyclopropene **6c**. The observed differences in the **2c** : **3c** ratios from reactions with **1c** and **6c** suggest that there may be some dependence on the carbene source among the catalysts employed for aromatic cycloaddition and C–H insertion, and that donor–acceptor cyclopropene **6c** and enoldiazoacetate **1c** may not form the same conformationally identical metal carbene intermediate. Use of a box ligand effectively inhibits dinitrogen extrusion from enoldiazoacetamide **1c**, but metal carbene formation from cyclopropene **6c** occurs without this limitation (entries 3 and 5). Other Lewis acids or under the thermal condition did not give any Buchner reaction or C–H insertion product, and only slowly decomposition of **6c** was observed (entries 8–11).

The assignment of relative stereochemistry for β-lactam **3** was made from ^{1}H NMR coupling constants,[21] and the observed *cis*-configuration is consistent with a steric influence of the catalyst attachments and rhodium surface on the aryl substituent of the intermediate metal carbene. The chiral Rh_2(*S*-PTTL)$_4$ catalyst was reported to exist in a crown conformation by Fox,[22] which means all of the ligands in an "all-up" orientation, and the bulky *t*-butyl and TBS substituents of the carbene are enclosed within the crown. This crowded transition state defines conformational preference for the aryl group to approach the carbene center for C–H insertion and the Buchner reaction. The (3*S*,4*R*)-configuration of the generated chiral centers in *β*-lactam **3** was confirmed by single-crystal X-ray diffraction analysis of **3i**, and the configurations of other compounds were assigned by analogy.[23]

Conclusions

In conclusion, we have discovered a highly selective asymmetric intramolecular C–H functionalization reaction of enoldiazoacetamides catalyzed by Rh_2(*S*-PTTL)$_4$ that occur *via* an intermediate donor–acceptor cyclopropene. The Buchner reaction was totally excluded in reactions catalysed by steric bulky dirhodium carboxylate catalyst, and β-lactam derivatives are obtained from intramolecular C–H insertion as one diastereoisomer in high yield with up to 99% enantiomeric excess. Furthermore, reactions of enoldiazoacetamides and their corresponding donor–acceptor cyclopropenes performed with copper(I) and silver(I) catalysts validate their formation of metal carbene intermediates, but they show differences in reactivity and selectivity. The high enantiocontrol that is achieved relies on both electronic and steric influences of the unique silylenol group in these metal carbene transformation.

Acknowledgements

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Notes and references

1 A. Fleming, *Rev. Infect. Dis.*, 1980, **2**, 129.
2 (*a*) E. Raviña, *The Evolution of Drug Discovery*, Wiley-VCH, Weinheim, Germany, 2011, pp. 254–272; (*b*) P. A. Magriotis, *Eur. J. Org. Chem.*, 2014, 2647; (*c*) C. R. Pitts and T. Lectka, *Chem. Rev.*, 2014, **114**, 7930; (*d*) S. France, A. Weatherwax, A. E. Taggi and T. Lectka, *Acc. Chem. Res.*, 2004, **37**, 592.
3 (*a*) J. W. Clader, *J. Med. Chem.*, 2004, **47**, 1; (*b*) M. A. Blazing, R. P. Giugliano, C. P. Cannon, T. A. Musliner, A. M. Tershakovec, J. A. White, C. Reist, A. McCagg, E. Braunwald and R. M. Califf, *Am. Heart J.*, 2014, **168**, 205; (*c*) S. D. Turley and J. M. Dietschy, *Curr. Opin. Lipidol.*, 2003, **14**, 233.
4 For reviews: (*a*) P. Galletti and D. Giacomini, *Curr. Med. Chem.*, 2011, **18**, 4265; (*b*) O. A. Pierrat, K. Strisovsky, Y. Christova, L. J. Jonathan, K. Ansell, N. Bouloc, E. Smiljanic and M. Freeman, *ACS Chem. Biol.*, 2011, **6**, 325; (*c*) P. A. Mann, *et al.*, *ACS Chem. Biol.*, 2013, **8**, 2442; (*d*) S. Vandekerckhove and M. D'hooghe, *Bioorg. Med. Chem.*, 2013, **21**, 3643.
5 (*a*) F. A. Davis, B. Yang and J. Deng, *J. Org. Chem.*, 2003, **68**, 5147; (*b*) R. Ratcliffe, T. Salzmann and B. Christensen, *Tetrahedron Lett.*, 1980, **21**, 31, intermolecular amide N–H insertion reactions: ; (*c*) E. C. Lee and G. C. Fu, *J. Am. Chem. Soc.*, 2007, **129**, 12066; (*d*) B. Xu, S. Zhu, X. Xie, J. Shen and Q. Zhou, *Angew. Chem., Int. Ed.*, 2011, **50**, 11483; (*e*) S. Chuprakov, B. T. Worrell, N. Selander, R. K. Sit and V. V. Fokin, *J. Am. Chem. Soc.*, 2014, **136**, 195.
6 Recent advances in asymmetric catalytic syntheses of β-lactam: (*a*) J. Pedroni, M. Boghi, T. Saget and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 9064; (*b*) S. R. Smith, J. Douglas, H. Prevet, P. Shapland, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.*, 2014, **79**, 1626; (*c*) Z. Chen, L. Lin, M. Wang, X. Liu and X. Feng, *Chem.–Eur. J.*, 2013, **19**, 7561; (*d*) L. Huang, W. Zhao, R. J. Staples and W. D. Wulff, *Chem. Sci.*, 2013, **4**, 622; (*e*) S. Chen, E. C. Salo, K. A. Wheeler and N. J. Kerrigan, *Org. Lett.*, 2012, **14**, 1784; (*f*) Y. S. M. Vaske, M. E. Mahoney, J. P. Konopelski, D. L. Rogow and W. J. McDonald, *J. Am. Chem. Soc.*, 2010, **132**, 11379.
7 (*a*) H. M. L. Davies and D. Morton, *Chem. Soc. Rev.*, 2011, **40**, 1857; (*b*) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (*c*) X. Cui, X. Xu, L. Jin, L. Wojtas and X. P. Zhang, *Chem. Sci.*, 2015, **6**, 1219; (*d*) D. N. Tran, C. Battilocchio, S. Lou, J. M. Hawkins and S. V. Ley, *Chem. Sci.*, 2015, **6**, 1120; (*e*) N. A. McGrath, K. A. Andersen, A. K. F. Davis, J. E. Lomax and R. T. Raines, *Chem. Sci.*, 2015, **6**, 752; (*f*) J. H. Hansen and H. M. L. Davies, *Chem. Sci.*, 2011, **2**, 457.
8 For review: (*a*) M. P. Doyle, Y. Liu and M. Ratnikov, *Org. React.*, 2013, **80**, 1; (*b*) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704; (*c*) M. P. Doyle, M. Ratnikov and Y. Liu, *Org. Biomol. Chem.*, 2011, **9**, 4007.

9 For reviews: (*a*) M. P. Doyle and D. C. Forbes, *Chem. Rev.*, 1998, **98**, 911; (*b*) P. M. P. Gois and C. A. M. Afonso, *Eur. J. Org. Chem.*, 2004, 3773.

10 (*a*) E. J. Corey and A. M. Felix, *J. Am. Chem. Soc.*, 1965, **87**, 2518; (*b*) S. D. Burke and P. A. Grieco, *Org. React.*, 1979, **26**, 361.

11 M. P. Doyle, M. N. Protopopova, W. R. Winchester and K. L. Daniel, *Tetrahedron Lett.*, 1992, **33**, 7819.

12 (*a*) M. P. Doyle and A. V. Kalinin, *Synlett*, 1995, 1075; (*b*) M. Anada, N. Watanabe and S. Hashimoto, *Chem. Commun.*, 1998, 1517; (*c*) N. R. Candeias, C. Carias, L. F. R. Gomes, V. André, M. T. Duarte, P. M. P. Gois and C. A. M. Afonso, *Adv. Synth. Catal.*, 2012, **354**, 2921.

13 A. Padwa, D. J. Austin, A. T. Price, M. A. Semones, M. P. Doyle, M. N. Protopopova, W. R. Winchester and A. Tran, *J. Am. Chem. Soc.*, 1993, **115**, 8669.

14 Advances in regioselectivity: (*a*) V. K. Lo, Z. Guo, M. K. Choi, W. Yu, J. Huang and C. Che, *J. Am. Chem. Soc.*, 2012, **134**, 7588; (*b*) J. P. Snyder, A. Padwa, T. Stengel, A. J. Arduengo, A. Jockisch and H. Kim, *J. Am. Chem. Soc.*, 2001, **123**, 11318; (*c*) P. M. P. Gois and C. A. M. Afonso, *Eur. J. Org. Chem.*, 2003, 3798; (*d*) C. H. Yoon, A. Nagle, C. Chen, D. Gandhi and K. W. Jung, *Org. Lett.*, 2003, **5**, 2259; (*e*) M. P. Doyle, M. S. Shanklin, S. Oon, H. Q. Pho, F. R. van der Heidet and W. R. Veal, *J. Org. Chem.*, 1988, **53**, 3384; (*f*) M. K. Choi, W. Yu and C. Che, *Org. Lett.*, 2005, **7**, 1081; (*g*) C. J. Moody, S. Miah, A. M. Z. Slawin, D. J. Mansfield and I. C. Richards, *J. Chem. Soc., Perkin Trans. 1*, 1998, 4067; (*h*) Z. Qu, W. Shi, X. Jin and J. Wang, *Chin. J. Org. Chem.*, 2003, **23**, 988; (*i*) L. A. Clarke, A. Ring, A. Ford, A. S. Sinha, S. E. Lawrencea and A. R. Maguire, *Org. Biomol. Chem.*, 2014, **12**, 7612.

15 For reviews: (*a*) X. Xu and M. P. Doyle, *Acc. Chem. Res.*, 2014, **47**, 1396; (*b*) X. Xu and M. P. Doyle, *Aust. J. Chem.*, 2014, **67**, 365, recent advances: ; (*c*) X. Xu, P. Y. Zavalij and M. P. Doyle, *Angew. Chem., Int. Ed.*, 2013, **52**, 12664; (*d*) X. Xu, P. Y. Zavalij and M. P. Doyle, *Angew. Chem., Int. Ed.*, 2012, **51**, 9829; (*e*) Y. Qian, X. Xu, X. Wang, P. Y. Zavalij, W. Hu and M. P. Doyle, *Angew. Chem., Int. Ed.*, 2012, **51**, 5900.

16 (*a*) X. Xu, P. Y. Zavalij and M. P. Doyle, *J. Am. Chem. Soc.*, 2013, **135**, 12439; (*b*) X. Xu, P. Y. Zavalij and M. P. Doyle, *Chem. Commun.*, 2013, **49**, 10287.

17 (*a*) P. Müller, Y. F. Allenbach and S. Grass, *Tetrahedron: Asymmetry*, 2005, **16**, 2007; (*b*) P. Müller, G. Bernardinelli, Y. F. Allenbach, M. Ferri and S. Grass, *Synlett*, 2005, 1397; (*c*) P. Müller, G. Bernardinelli, Y. F. Allenbach, M. Ferry and H. D. Flack, *Org. Lett.*, 2004, **6**, 1725.

18 Nonpolar solvents provide a significant increase in the enantioselectivity in some metal carbene reactions, for example, 2,2-DMB and TBME have previously been demonstrated to be an optimal solvent for enantioselective C–H functionalization and other metal carbene transformations: (*a*) H. Wang, G. Li, K. M. Engle, J. Yu and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 6774; (*b*) A. G. Smith and H. M. L. Davies, *J. Am. Chem. Soc.*, 2012, **134**, 18241; (*c*) X. Wang, X. Xu, P. Y. Zavalij and M. P. Doyle, *J. Am. Chem. Soc.*, 2011, **133**, 16402.

19 The *cis* isomer was not detected, even at short reaction times.

20 M. Díaz-Requejo and P. J. Pérez, *Chem. Rev.*, 2008, **108**, 3379.

21 The relative chemistry could be distinguished by ^{1}H NMR coupling constants, see ref. 14*e*: generally *cis* = 5–8 Hz; *trans* = 0–2 Hz.

22 (*a*) A. DeAngelis, O. Dmitrenko, G. P. A. Yap and J. M. Fox, *J. Am. Chem. Soc.*, 2009, **131**, 7230; (*b*) S. Hashimoto, N. Watanabe, T. Sato, M. Shiro and S. Ikegami, *Tetrahedron Lett.*, 1993, **34**, 5109; (*c*) D. T. Boruta, O. Dmitrenko, G. P. A. Yap and J. M. Fox, *Chem. Sci.*, 2012, **3**, 1589.

23 ESI.†