Rh/Lewis Acid Catalyzed Regio-, Diastereo- and Enantioselective Addition of 2-Acyl Imidazoles with Allenes

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A highly regio-, diastereo- and enantioselective addition of 2-acyl imidazoles or 2-acyl pyridines with allenes promoted by Rh/Lewis acid synergistically catalytic system is described. This atom economic approach leads to the formation of the branched allylic alkylated products including acyclic quaternary all-carbon stereogenic centres in good yields with good to excellent diastereo- and enantioselectivities. Kinetic studies reveal that the rate-determining step in this process is the oxidative addition of Rh(I) with C-H bond.

Keywords rhodium, allene, enantioselective, Lewis acid, allylation

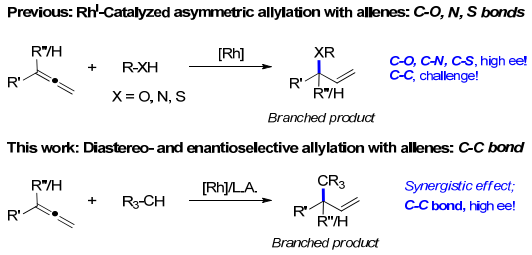
Introduction

Transition metal catalyzed allylic alkylation is considered as one of the most standout success of transition metal catalysis, enjoys tremendous popularity for the construction of carbon-carbon bonds along with wide applications in the synthesis of numerous pharmaceutical and natural products.[1] Although a myriad of powerful methods including the asymmetric versions have been developed by varying the substrates, nucleophiles and metal complexes over the years,[2-5] these methods are less attractive in terms of atom economy, requires specially designed substrates and generates waste.

Following on the pioneering work by the Trost[6] and Yamamoto[7] with palladium catalysts, Breit and co-workers[8-10] developed a series of rhodium-catalyzed pro-nucleophile addition reactions to allenes and terminal alkynes towards enantio-enriched branched allylic products, which can be regarded as atom-economic alternatives to traditional allylic substitution.[11] This strategy was successfully explored towards a number of asymmetric C-X (O, N, S) bonds formation to achieve enantio-enriched branched allylic products (Scheme 1). However, rhodium catalyzed asymmetric addition of carbon pronucleophiles to allenes remains a formidable challenge,[12] which might be due to the relatively weak acidity of C-H bond, hindering the oxidative addition with rhodium complexes.[13]

To address the above challenge, we envisioned to activate the carbon pronucleophile by: (a) employing compatible Lewis acid[14] to improve the acidity of C-H bond; (b) installing an appropriate chelating group[15] to form relative stable rhodacycle to facilitate the oxidative addition of C-H with the Rh(I) complex. Further, we have also anticipated that the formation of relatively stable rhodacycle with rigid framework could facilitate the enantio-induction of this transformation. To examine our hypothesis, 2-acyl imidazole[16] **2a** was selected as model substrate for the asymmetric coupling with allene.[17]

Scheme 1 Rh-catalyzed approaches towards asymmetric allylation with allenes



Experimental

In a 10 mL flame dried schlenk tube fitted with a rubber septum and magnetic bar, 2-acyl imidazole (0.15 mmol, 1 equiv) was added and put on vacuum and backfilled with argon for three times. Then, the schlenk tube was transferred to glove box and $[Rh(COD)Cl]_2$ (3 mg, 0.006 mmol, 4 mol%), (*S*)-SEGPHOS (11 mg, 0.018 mmol, 12 mol%) and $Yb(OTf)_3 \cdot H_2O$ (9 mg, 0.015 mmol, 10 mol%) were added. The tube was then removed from the glove box and 0.75 mL of anhydrous dichloroethane (DCE) and allene (0.3 mmol, 2.0 equiv) were added by syringe under a flow of argon and stirred at 40 °C for 48-72 hours. After completion of the reaction (as monitored by TLC analysis), the reaction mixture was directly purified with column chromatography

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Received ((will be filled in by the editorial staff)); accepted ((will be filled in by the editorial staff)); published online XXXX, 2017.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.2017xxxxx or from the author. ((Please delete if not appropriate.)).
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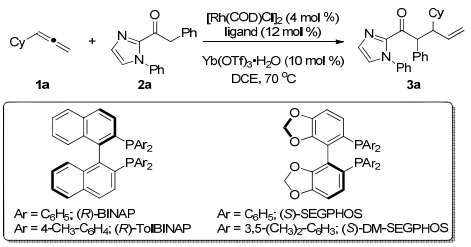
on silica gel, eluting with 0-7% EtOAc in PE (elution gradient).

Results and Discussion

We emanated our study by exploring effective combination of chiral ligand, Lewis acid and reaction conditions for the regio-, diastereo- and enantioselective coupling of cyclohexylallene **1a** and 2-acyl imidazole **2a** (Table 1). In the presence of 4 mol% of $[Rh(COD)Cl]_2$, 12 mol% of (*R*)-BINAP and 10 mol% of $Yb(OTf)_3 \cdot H_2O$, the reaction of **1a** and **2a** in DCE at 70 °C took place to furnish the branched allylic product **3a** in 84% yield with 78:22 dr and 82:18 er (entry 1, Table 1). Encouraged by this promising result, we screened various phosphine ligands (entries 2-4). Among the ligands tested, (*S*)-SEGPHOS was found to be most competent, affording **3a** in 89% yield with 80:20 dr and 93:7 er (entry 3). Pleasingly, lowering the reaction temperature to 40 °C led to improved diastereo- and enantioselectivity (85:15 dr, 93:7 er, entry 5). Following further screening of chiral ligands, Lewis acids, solvents and metal catalysts (see Supporting Information for more details, Table S1-S4). Lewis acids such as $Sc(OTf)_3$, $In(OTf)_3$, $Mg(OTf)_2$ and $Cu(OTf)_2$ have no significant impact on the outcome of the title reaction. The optimal reaction conditions were identified as following: 4 mol% of $[Rh(COD)Cl]_2$, 12 mol% of (*S*)-SEGPHOS and 10 mol% of $Yb(OTf)_3 \cdot H_2O$ in DCE (0.2 M) at 40 °C.

Table 1 Optimization of reaction conditions[a]

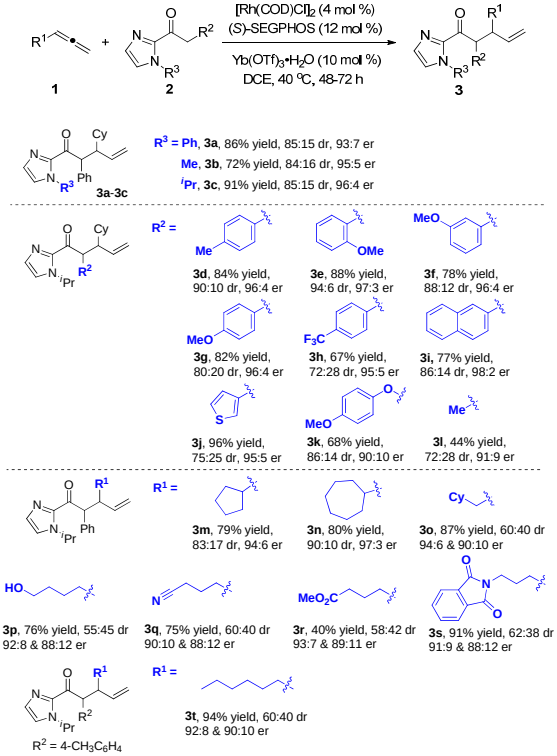


Entry	Ligand	Yield (%)[b]	dr [c]	er[d]
1	(R)-BINAP	84	78:22	18:82
2	(R)-TolBINAP	76	77:23	19:81
3	(S)-SEGPHOS	89	80:20	93:7
4	(S)-DM-SEGPHOS	90	79:21	83:17
5	(S)-SEGPHOS	86	85:15	93:7

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), $[Rh(COD)Cl]_2$ (4 mol%), ligand (12 mol%) and $Yb(OTf)_3 \cdot H_2O$ (10 mol%) in DCE (1 mL) at 70 °C for 48 h under argon, unless otherwise noted. [b] Isolated yield. [c] Diastereoselectivity (dr) was determined by ^1H NMR analysis of the crude reaction mixture. [d] Enantioselectivity (er) of the major diastereomers were determined by HPLC analysis. [e] Carried out at 40 °C. [f] 0.5 mL DCE was used.

With the optimized conditions in hand, the scope of the reaction with regard to both the 2-acyl imidazoles and allenes were examined (Scheme 2). The 2-acyl imidazoles with different *N*-substitution afforded the desired branched allylic products (**3a-3c**, Scheme 2) in good yields with excellent enantioselectivities (93:7-96:4 er). Similarly, 2-acyl imidazoles with either electron-rich or electron-poor aryl groups also furnished the corresponding products (**3d-3g**, **3h**) in good yields with consistently high enantioselectivities. In addition, 2-acyl imidazoles incorporating 2-naphthyl or thienyl group were similarly good coupling partners to afford **3i** (77% yield, 86:14 dr, 98:2 er) and **3j** (96% yield, 88:12 dr, 95:5 er), respectively. Notably, ether and alkyl substituted 2-acyl imidazoles were also tolerated in our optimal reaction conditions to give the corresponding adduct with slightly decreased enantioselectivities (**3k** and **3l**). In addition to cyclohexylallene, other α-alicyclic allenes were also proved to be excellent coupling partners to afford the desired allylic products in high yields with excellent enantioselectivities (**3m** and **3n**, Scheme 2). Linear-alkyl-substituted allenes and allenes with different functional group such as free alcohol, cyano, ester, ptthalimino also performed well under the optimal reaction conditions in terms of yields and enantioselectivities (**3o-3t**), however relatively lower diastereoselectivities were observed.

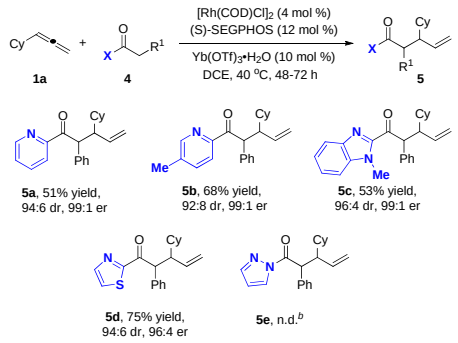
Scheme 2 Rh-catalyzed approaches towards asymmetric allylation with allenes[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.15 mmol), $[Rh(COD)Cl]_2$ (4 mol%), (*S*)-SEGPHOS (12 mol%) and $Yb(OTf)_3 \cdot H_2O$ (10 mol%) in DCE (0.75 mL) at 40 °C for 48-72 h under argon. Yield of isolated products were reported. Diastereoselectivity (dr) was determined by ^1H NMR analysis of the crude reaction mixture. Enantioselectivity (er) of the major diastereomers were determined by HPLC analysis.

Then, we sought to examine different chelating groups for this transformation (Scheme 3). Pleasingly, the reaction of 2-acyl pyridine **4a** with cyclohexylallene **1a** proceeded smoothly to afford the desired branched allylic product **5a** in 77% yield, 94:6 dr and 99:1 er. The 2-acyl pyridines with methyl in the pyridine moiety also delivered the corresponding product **5b** in 68% yield with 99:1 er. Moreover, benzimidazole and 2-thiazole were found to be good chelating group for the title reaction, affording the corresponding products with excellent diastereo- and enantioselectivities (**5c** and **5d**). However, 1-acyl pyrazole could not be tolerated under the optimized conditions, the reaction with cyclohexylallene led to the formation of a complex mixture without detecting the formation of **5e**. The absolute configuration of major diastereomer of product **5b** was confirmed by a single-crystal X-ray analysis (for details, see the Supporting Information).[18]

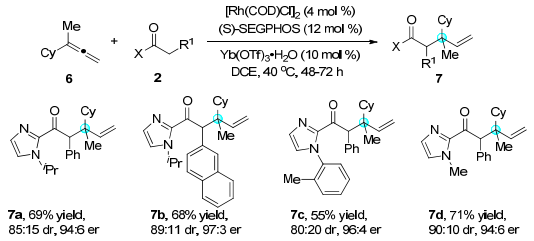
Scheme 3 Investigation of effect of chelating groups[a]



[a]Reaction conditions: **1a** (0.3 mmol), **4** (0.15 mmol), $[Rh(COD)Cl]_2$ (4 mol%), (*S*)-SEGPHOS (12 mol%) and $Yb(OTf)_3{\cdot}H_2O$ (10 mol%) in DCE (0.75 mL) at 40 °C for 48-72 h under argon. Yield of isolated products were reported. Diastereoselectivity (dr) was determined by ^1H NMR analysis of the crude reaction mixture. Enantioselectivity (er) were determined by HPLC analysis. [b]Formation of unidentified complex mixture.

Next, we wished to explore our approach for the asymmetric synthesis of synthetically challenging acyclic quaternary all-carbon stereogenic centres (Scheme 4). In order to achieve enantioselective formation of acyclic quaternary all-carbon stereogenic centres, the catalytic systems need to overcome the high degree of steric repulsion between the carbon substituents along with the conformational control.[19,20] Gratifyingly, the coupling reactions of 1-methyl-1-cyclohexyl allene **6** with various of 2-acyl imidazoles **2** furnished **7a-7d** in 55-71% yield with 94:6-97:3 er.

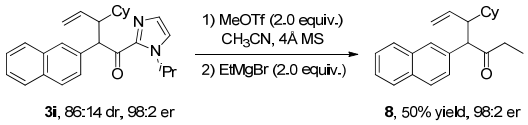
Scheme 4 Synthesis of acyclic all-carbon quaternary centres[a]



[a]Reaction conditions: **6** (0.3 mmol), **2** (0.15 mmol), $[Rh(COD)Cl]_2$ (4 mol%), (*S*)-SEGPHOS (12 mol%) and $Yb(OTf)_3{\cdot}H_2O$ (10 mol%) in DCE (0.75 mL) at 40 °C for 48-72 h under argon. Yield of isolated products were reported. Diastereoselectivity (dr) was determined by ^1H NMR analysis of the crude reaction mixture. Enantioselectivity (er) were determined by HPLC analysis.

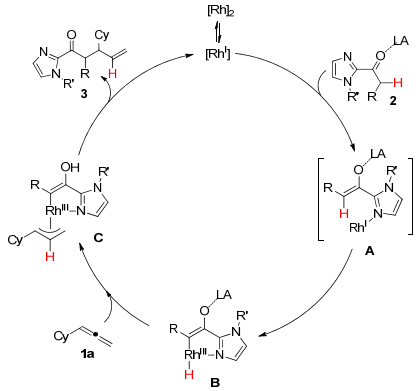
To illustrate the potential synthetic application of this protocol, further transformation of the product was carried out. The imidazole moiety could be easily transferred to other functional groups. For example, the removal of the imidazole moiety of **3i** worked smoothly, resulting in ketone **8** (major diastereomer) in 50% yield without loss in enantiomeric excess (Scheme 5).

Scheme 5 Synthetic transformation of product **3i**



A plausible mechanism is shown in Scheme 6. Lewis acid and chelation assisted oxidative C-H addition of 2-acyl imidazole to Rh(I) via a transient species **A**, generates a Rh(III)-H intermediate **B**. Then, hydrometalation of the allene with intermediate **B** leads to the formation of intermediate **C**,[21] which might be attacked by another molecule of 2-acyl imidazole or perform reductive elimination to furnish the branched product **3**.

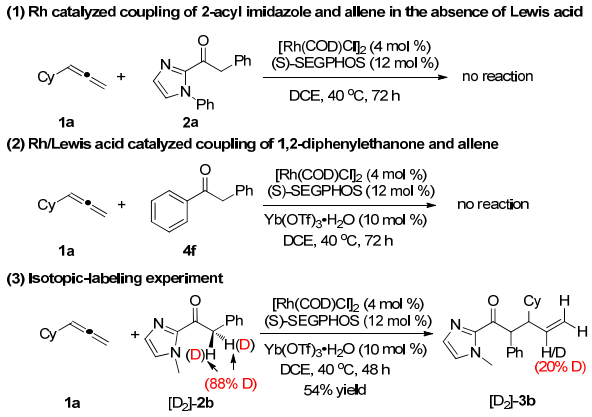
Scheme 6 Proposed mechanism



Control Experiments. To gain a better understanding of the mechanistic details of this reaction, several control experiments (Scheme 7) and initial rate kinetics experiments were performed. The coupling reaction of

cyclohexylallene and 2-acyl imidazole **2a** did not proceed in the absence of Lewis acid (eqn 1, Scheme 7), suggesting that the Lewis acid is an indispensable component of the catalytic system. Similarly, the reaction of cyclohexylallene and substrate **4f** without chelating group also failed to proceed, which affirmed the requisite of chelating group for the title reaction (eqn 2, Scheme 7). From these two experiments it appears that both the Lewis acid and chelating group in pronucleophile synergistically assist the reaction to proceed. An isotope-labeling experiment was performed with [D_2]2-acylimidazole and cyclohexylallene under the optimal reaction conditions (eqn 3, Scheme 7). The deuterium incorporation was observed only at the internal position of the alkene (see Supporting Information for more details).

Scheme 7 Control experiments



Kinetic experiments and NMR Monitoring Experiment. Moreover, initial rate kinetic experiments were performed to elucidate the reaction order for the Rh catalyst and for both the allene and 2-acyl imidazole by in situ ^{1}H NMR spectroscopy. The reaction appeared to have a first-order dependence on the Rh precatalyst and substrate **2c** (Figure 1-2), and a nearly zero-order dependence on substrate **1a** (Figure 3, see Supporting Information for more details). The first-order dependence on the Rh catalyst and substrate **2c** indicates that Rh and **2c** are involved in rate-limiting step. The zero-order dependence of the substrate **1a** shows that substrate incorporation into the catalytic cycle is not rate-limiting. These experiments are consistent with a pathway wherein the rate-determining step occurs prior to intermediate **B** addition to the allene. Moreover, as shown in Scheme 8, a primary KIE of 2.45 was found for 2-acyl imidazole with proton vs deuterium labels at the α-carbonyl position. To investigate if the oxidative addition of Rh(I) with C-H bond is rate-limiting, we performed a Hammett plot study of para-substituted 2-acyl imidazoles (Figure 4), in which electron-donating substrate led to a higher initial rate. These investigations provide insight that the oxidative addition of Rh(I) with C-H bond might be rate-determining step under these catalytic conditions. The NMR monitoring experiment of stoichiometric amount of 2-acyl imidazole with [Rh(COD)Cl]$_2$, Sc(OTf)$_3$ and (*S*)-SEGPHOS in $CDCl_3$ was conducted. The ^{1}H NMR spectrum (263K) of the reaction after 10 minutes reaction at 30 °C showed a major Rh-H species at δ = -16.3 ppm, which indicates the oxidative addition of the C-H bond to the rhodium.

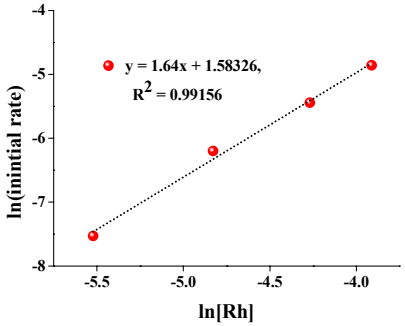


Figure 1 Plot of initial rate versus [Rh] (M).

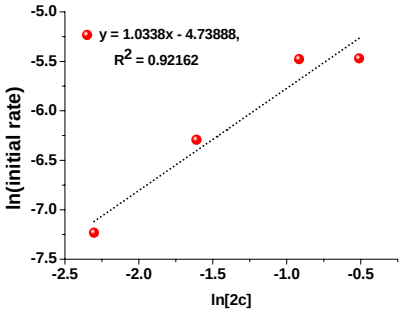


Figure 2 Plot of initial rate versus [2-acyl imidazole **2c**] (M).

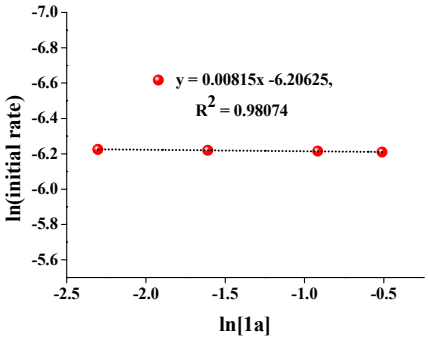


Figure 3 Plot of initial rate versus [allene **1a**] (M).

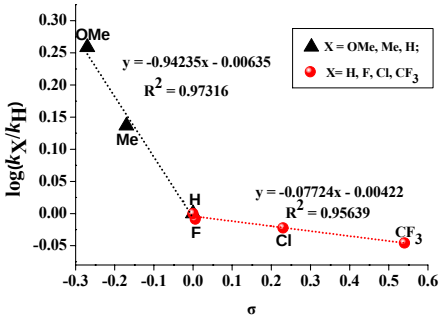
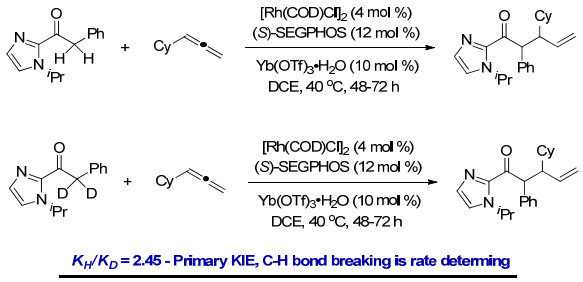


Figure 4 Hammett-plot of para-substituted 2-acyl imidazoles.

Scheme 8 Control experiments



Conclusions

In summary, we have successfully demonstrated an atom economic approach for asymmetric allylic alkylation of 2-acyl imidazoles or 2-acyl pyridines with allenes promoted by the combination of rhodium and Lewis acid catalysis. The reaction produced the branched allylic alkylated products in good yields with good to excellent diastereo- and enantioselectivities. This approach was also explored for the enantioselective construction of synthetically challenging acyclic quaternary all-carbon stereogenic centres. The mechanistic studies including of control experiments and initial rate kinetic experiments indicate that 1) both the Lewis acid and chelating group assisted C-H oxidative addition to Rh-complex is a key step to accomplish the anticipated coupling; 2) the oxidative addition of Rh(I) with C-H bond might be rate-determining step under the optimal reaction conditions. Further extension of the protocol with other coupling partners are currently underway in our laboratory.

Acknowledgement

We thank Prof. Daqiang Yuan (Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences) for his kind help in an X-ray analysis. This work was supported by the Strategic Priority Research Program of the Chinese Academy of Sciences, Grant No. XDB20000000 and 100 Talents Programme of the Chinese Academy of Sciences.

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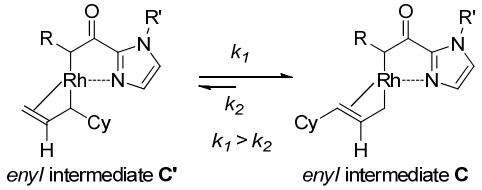
[21] Hydrometalation of allene with intermediate **B** might generate enyl intermediate **C'**, which undergoes isomerization to **C** in competition with alkylation. We prefer to rule out this pathway due to the linear product wasn't observed in our catalytic system. For pioneer investigation of enyl organorhodium intermediate, see ref. **4b**.



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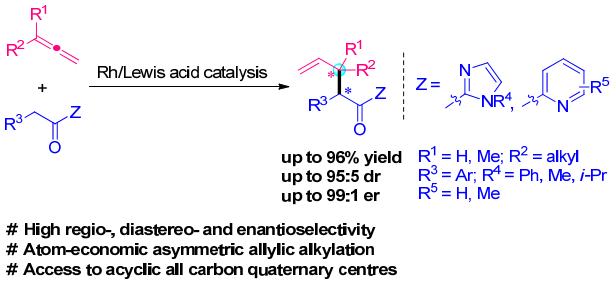

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A highly regio-, diastereo- and enantioselective addition of 2-acyl imidazoles or 2-acyl pyridines with allenes promoted by Rh/Lewis acid synergistically catalytic system is described which leads to the formation of the branched allylic alkylated products including acyclic quaternary all-carbon stereogenic centres in good yields with good to excellent diastereo- and enantioselectivities.