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Dynamic kinetic resolution during iron carbonyl promoted [6+2] ene-type reactions

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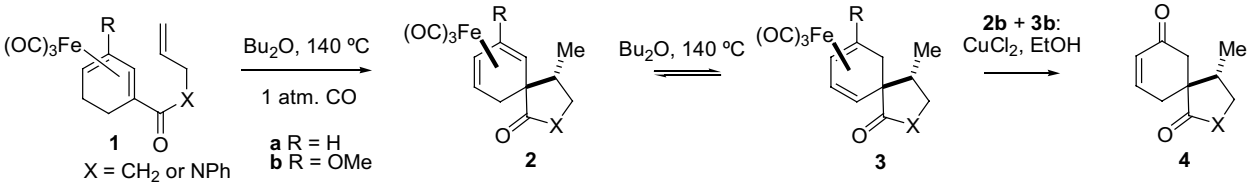
Abstract—Intramolecular coupling of cyclohexadiene–$Fe(CO)_3$ complexes with pendant alkenes, to form spirolactams, proceed with excellent stereocontrol, using chiral amide substrates that lead to dynamic kinetic resolution.

Transition metal promoted cyclocoupling reactions of alkenes have a rich history, and occupy an important place in organic synthesis methodology.[1] These processes often complement their more traditional organic counterparts in terms of stereochemistry and our ability to carry out reactions that are symmetry forbidden, or compromised by more facile competing processes. While such transformations in the coordination sphere of a metal are often not concerted single-step reactions, they are nevertheless usually stereospecific, a result of continual attachment of the reacting ligand(s) as the key bond-forming steps proceed.

We have developed a novel coupling reaction between a diene–$Fe(CO)_3$ complex and a pendant alkene, that is equivalent to a [6+2] ene reaction.[2] While this is a non-concerted transformation, the key bond-forming event is nevertheless stereospecific, as illustrated in Scheme 1. The initial product from amide **1** is lactam **2**, but this undergoes rearrangement of the diene–$Fe(CO)_3$ system, via a hydride shift, to afford **3** under the reaction conditions. Thus, when R = H in the simple case illustrated, a mixture of epimers **2a** and **3a** is obtained. We have developed a number of approaches to control the stereochemical outcome of this reaction, one of which uses a methoxy substituent on the diene (R = OMe, **1b**). In this case a mixture of regioisomers **2b/3b** is generated, but removal of the metal, followed by hydrolysis of the resulting mixture of dienol ethers affords a single enone **4**.[3]

Another problem that arises with the unsubstituted series (R = H) is that the same thermal rearrangement that converts **2** to **3** also occurs with the reactant **1**, in that case leading to racemization of optically pure complexes. This too has been overcome by attaching suitable substituents to the cyclohexadienyl ring,[4] but it also provides an avenue for dynamic kinetic resolution in cases where the pendant alkene has a stereogenic centre, which is the subject of this Letter.

Consider the reaction shown in Scheme 2. If there is a significant difference in the rates of cyclization of the two diastereomers **5** and **6** (**5** being faster), compared



Scheme 1.

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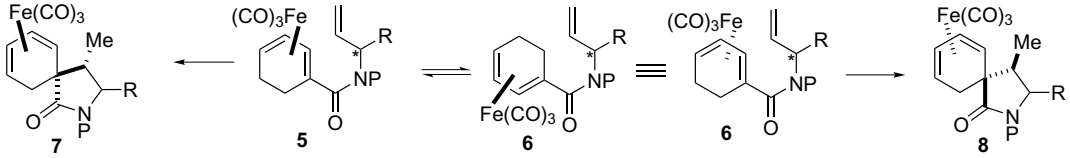


Scheme 2.

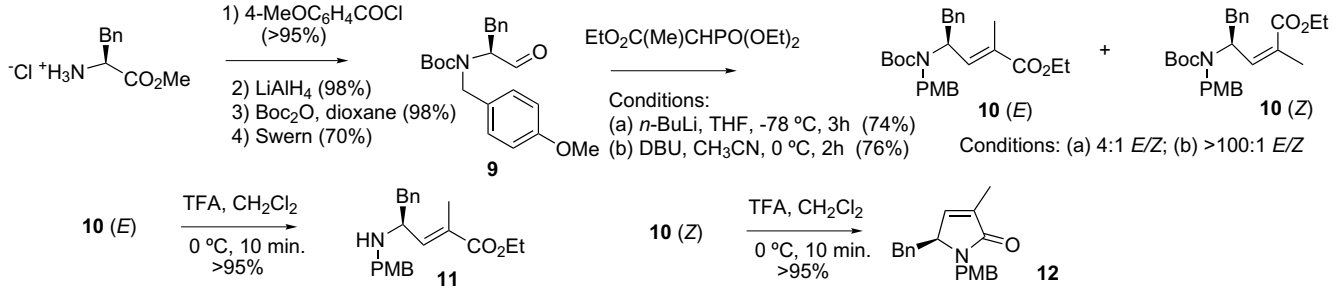
with their rate of interconversion (which occurs by iron-mediated hydride transfer), then we should observe predominant formation of **7** over **8**. Indeed, if the equilibration between **5** and **6** is sufficiently facile, and the cyclization rates are greatly different, a mixture of these two complexes might afford a single product. Note that the diene–$Fe(CO)_3$ unit in **6** is enantiomeric with that in **5** (see the alternate drawing of **6**, which is derived by rotation about the diene–carbonyl C–C bond). Of course, **7** will undergo the same rearrangement as noted for **2**, but this is also a controllable event.[5] Should this process occur as proposed, then the newly generated stereocentres are controlled by the stereochemistry at C*, and the requisite amide can be prepared from a *racemic* cyclohexadienoic acid complex.

The amide derivatives (X = NR) are chosen for illustration here because the requisite amines can be prepared from the corresponding readily available amino acids. We also chose to use a trisubstituted pendant alkene unit, for reasons that will become apparent later in the discussion. For this purpose, we required amine derivative **11**, which was prepared from phenylalanine as outlined in Scheme 3. Thus, the protected amino aldehyde **9** was prepared using a literature procedure,[6] and subjected to Horner–Wadsworth–Emmons reaction under two sets of reaction conditions. The phosphonyl enolate derived by treatment of the precursor phosphonoester with *n*-BuLi afforded a mixture of *E* and *Z* alkenoic esters **10** favouring the *E* isomer, but in only a 4:1 ratio, though these can be separated chromatographically. Use of DBU/LiCl[7] produced essentially single *E* isomer in good yield. N-Deprotection of (*E*)-**10** afforded **11**. It should be noted that the minor (*Z*) isomer from the BuLi-promoted reaction underwent spontaneous formation of lactam **12** on deprotection, as expected, so our study of the [6+2] ene cyclization reaction was confined to the *E* isomer at this time.

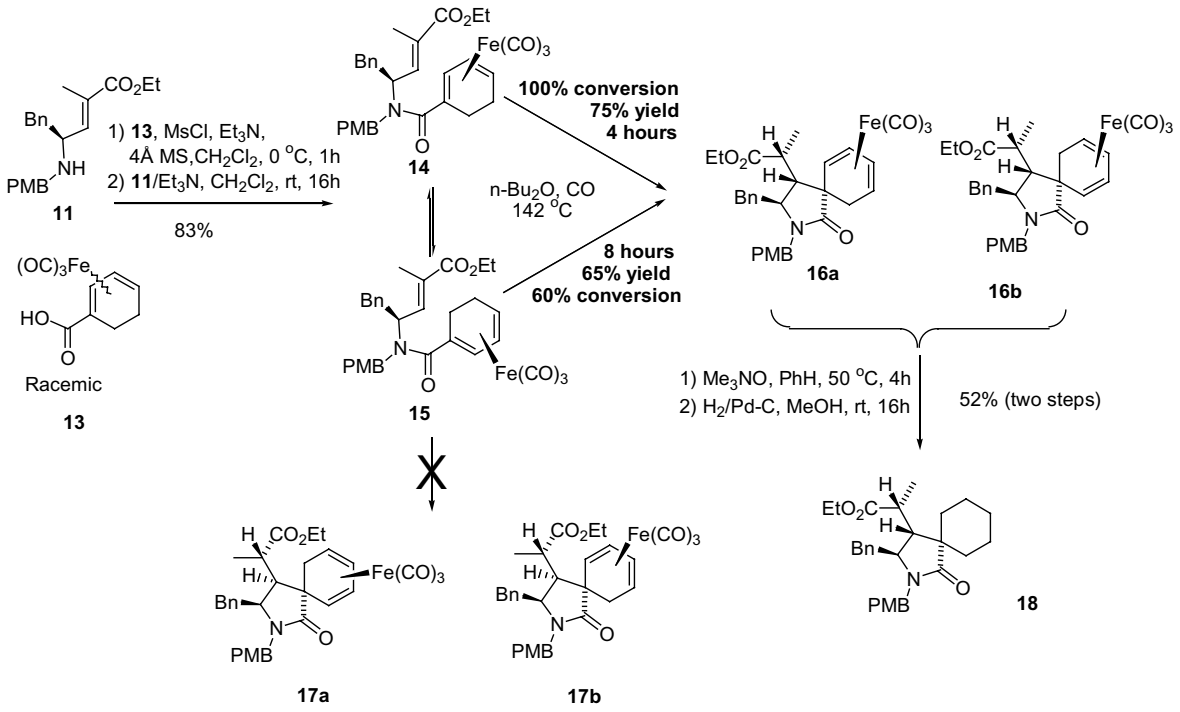
The chiral trisubstituted amino ester **11** was coupled with the racemic acid **13**, via its acyl mesylate, to produce a pair of diastereomeric amides, **14** and **15**, which were separated (Scheme 4). Complex **14** was also prepared from the amine and enantiomerically pure acid of known stereochemistry,[8] which allowed unambiguous structural assignment of **14** and **15**. Cyclization of **14** gave a 1:1 mixture of epimeric spirolactams **16** in 75% isolated yield (4 h, 100% conversion; minor by-products appear to be from demetallation of **16**). It should be noted that, according to our earlier observations on this reaction, **16a** is the initial product and this undergoes thermal rearrangement to give **16b**. Direct cyclization of **15** did not afford *any* of the products **17**. Instead, upon heating **15** rearranged to give its diastereomer **14**, which then cyclized to give products **16** in 65% yield (8 h, 60% conversion). Cyclization of a 1:1 mixture of **14** and **15** gave the same pair of epimers **16** in 63% isolated yield. The much slower cyclization of **15** compared with **14** is consistent with the proposition that complex **15** must undergo rearrangement of the diene, to form **14** first. The mixture of epimeric lactams **16** was demetallated (Me_3NO), followed by hydrogenation to give a single product **18**, thus confirming that efficient dynamic kinetic resolution indeed occurs.

The difference in reactivity between **14** and **15** can be rationalized by considering the strain energies of putative intermediates, which can be calculated by molecular mechanics using PC Spartan. According to the mechanism, **14** and **15** have to be converted to the intermediates **18** and **19**, respectively. Intermediate **18** is lower in energy than **19** by 1.8 kcal/mol. Formation of **19** from **15** is therefore likely to be slow compared with isomerization of **15** to **14**, which prevents formation of **17a**. At the same time, conversion of **14** to **18** occurs more easily and **18** then cyclizes to form **16a**.

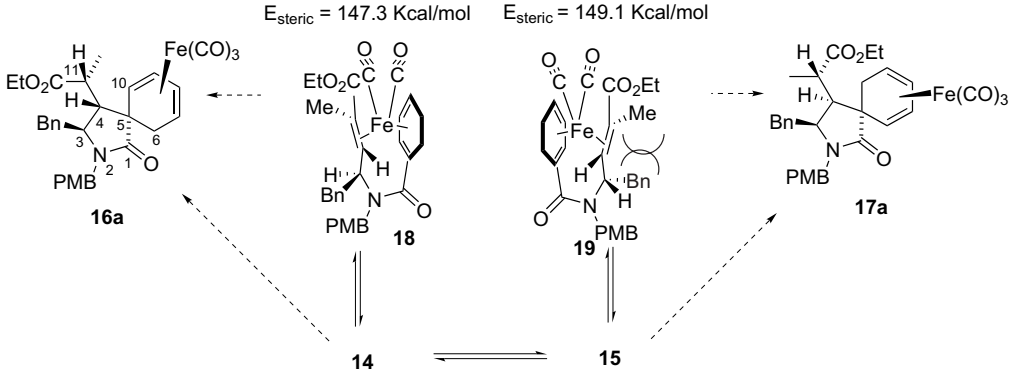
As mentioned earlier, we considered that a trisubstituted alkene residue would be needed for efficient dynamic kinetic resolution. This supposition was based on the fact that intermediate **19** has a destabilizing non-bonded interaction between the methyl and benzyl groups, as



Scheme 3.

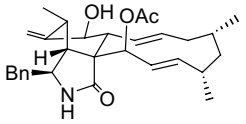


Scheme 4.



Scheme 5.

indicated on the structure. This interaction is absent in intermediate **18** (note that steric interaction with the ester residue is not possible because of the double bond stereochemistry). In fact, we have observed that similar complexes lacking the methyl substituent give much poorer selectivity (ca. 2.5:1), but these results are not included here because mixtures of four diastereomers were generally obtained (analogous to diastereomers **16a/b** and **17a/b** in Scheme 5), and the products were not fully characterized.



18-deoxycytochalasin H

In summary, it is possible to use a chiral amide substituent to drive the stereochemical outcome of the iron promoted [6+2] ene-type reaction in a single direction by dynamic kinetic resolution. Multiple stereogenic centres can be produced in a single enantiomeric form. This chemistry is interesting because of the similarity between the spirolactam structure **18** and cytochalasin structures such as the HIV protease inhibitor 18-deoxycytochalasin H,[9] though the stereochemistry of this molecule would require us to use the amide derived from the *Z* isomer of **11**. Future work will examine methods to prepare this system and its cyclization, as well as tandem reactions that are analogous to those described earlier,[5] that will afford multicyclic structures derived only from **16a**, which avoids the problem of **16a/16b** mixture formation.

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Supplementary data

Spectroscopic data for all new compounds reported. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.166.

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