Synthesis of the Taxol Core via Catalytic Asymmetric 1,4-Addition of an Alkylzirconium Nucleophile

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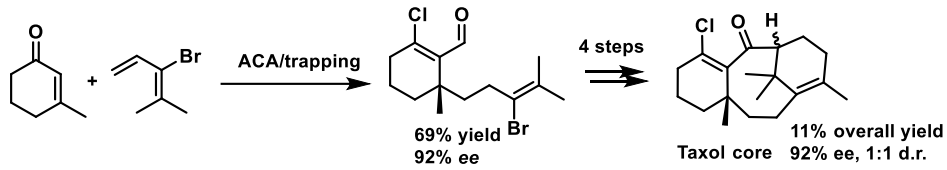
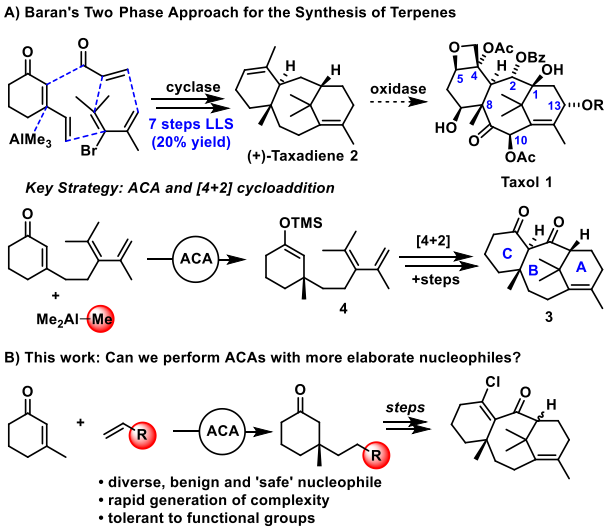
Supporting Information Placeholder



ABSTRACT: The Taxol core was prepared in five steps via a key copper-catalyzed asymmetric conjugate addition (ACA) trapping sequence. The use of a bromodiene derived alkylzirconium nucleophile followed by trapping with $POCl_3$/DMF give a highly functionalized intermediate featuring a quaternary centre in 69% yield and 92% ee. After 1,2-addition, Suzuki-Miyaura cross coupling, allylic oxidation, and a type II intramolecular Diels-Alder reaction the taxol core was obtained in 11% overall yield with 92% ee.

Taxol **1** (trademarked as Paclitaxel) is a multi-billion dollar anticancer drug. In the past, interest in this molecule stemmed from solving an issue of supply; Taxol was only available in appreciable quantities from the Yew tree and harvesting from such a source was not sustainable.[1a] A significant effort was devoted toward the chemical synthesis of **1** and many advances in organic chemistry were made by groups attempting to solve this challenging problem.[1b-j]

Scheme 1. A) Synthesis of (+)-Taxadiene by Baran and co-workers B) This work



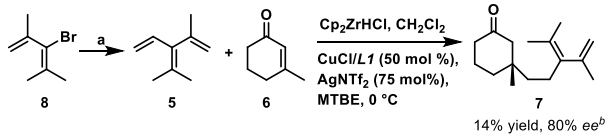
A recent strategy for the synthesis of terpenes proposed by Baran and co-workers involves first constructing the carbon-based framework of the molecule, followed by the installation of functional groups via a series of late stage oxidations to give the target.[2a-c] Using this approach, oxidized Taxanes including Taxol itself were prepared by the combination of a "cyclase" phase to form the carbon skeleton, followed by an "oxidase" phase to adjust the final oxidation state of the molecule (Scheme 1, **A**).[2d-e] Thus, the cyclase phase was implemented to provide Taxadiene **2** in 7 steps and 20% overall yield. The brevity in the synthesis of **2** arises from two key features (Scheme 1, **B**); the use of a Type II intramolecular Diels-Alder reaction to prepare the A/B rings of **3,** a strategy shared by Shea and others to prepare Taxane derivatives,[3] and a catalytic asymmetric conjugate addition (ACA) for the formation of **4** using Alexakis's protocol for Me-addition.[4]

The latter of these tactics was the main inspiration for this project and we wondered if we could add fragments more complex than simple alkyl units such as methyl (Scheme 1, **C**). The nucleophiles traditionally used in ACAs (organozinc, organoaluminum and Grignard reagents)[5] are limited to only very simple coupling partners. Further, the use of these organometallic reagents imposes limits on which functional groups can be used and the applicability of these procedures in complex molecule synthesis. In 2013, we reported the formation of quaternary stereogenic centers[6] by ACA of alkylzirconium reagents[7] to enones.[8] The transformations are catalyzed by copper-phosphoramidite complexes and the alkyl zirconocenes are generated in situ from alkenes and Cp_2ZrHCl via hydrometallation. Alkylzirconium reagents, when used in this fashion, can mitigate the aforementioned shortcomings of traditional nucleophiles since they are more tolerant towards functional groups. We hoped to use an appropriate fragment in a synthesis of the taxol core but the precise choice of the precursor alkene was not immediately obvious. Also, it is more common than not, that ACAs are sensitive to solvent, tempera-

ture, concentration, method of addition and presence of additives.[5]

In an approach that would have closely follow Baran's route to the core, conjugated triene **5**[9] was added to **6** (Scheme 2). Despite extensive optimization, **7** could only be obtained in 14% yield and 80% *ee*. Although disappointing, no side products that would result from hydrozirconation at the di- or tetrasubstituted olefins were observed and we postulated that the low yield was due to the size of the polyene.

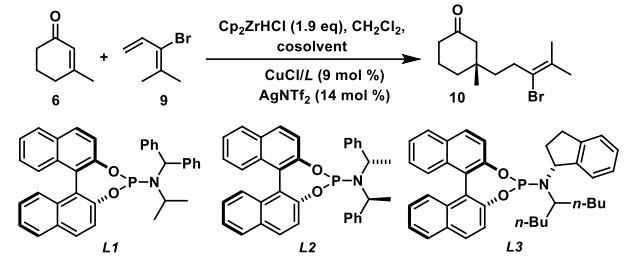
Scheme 2. Preparation of Intermediate **7** using ACA of Triene **5**



a) Vinylmagnesium bromide (1.3 eq.), $ZnBr_2$ (2.0 eq.), $PdCl_2$.dppf (0.020 eq.), THF 0 °C to rt 6.5 h, 49%; b) ee determined by SFC or HPLC. *Abbreviations: dppf = 1,1'-Bis(diphenylphosphino)ferrocene*

In our search for an alkene with a smaller steric profile, we encountered bromodiene **9**[10] first reported by Takahashi and co-workers. **9** was prepared from 3-methylcrotonaldehyde via bromination to the corresponding bromoaldehyde, followed by Peterson olefination and could easily be made on a decagram scale (see supporting information for more details).

Table 1. Optimisation of Key ACA Conjugate Addition Step



entry	L	cosolvent	yield[a] (%)	*ee*[b] (%)
1	1	MTBE	70	6
2	2	MTBE	63	18
3	3	MTBE	81	82
4	**3**	**DCE**	**45**	**90**
5	3	PhMe	71	88

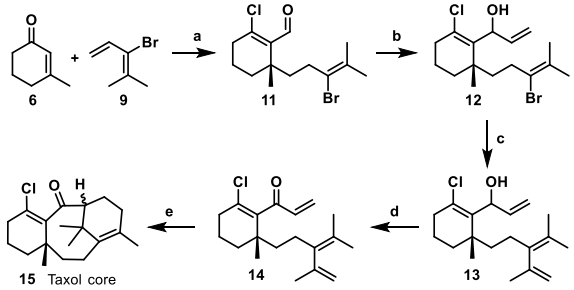
*Reactions were performed on 0.5 mmol scale using 2.4 eq **9**. a) isolated yields; b) ee's were determined by SFC or HPLC analysis using a chiral non-racemic stationary phase.

The ACA of **9** to **6** was examined and it was found that the phosphoramidite ligand has a tremendous effect on enantioselectivity of this reaction (Table 1). **L1** and **L2** have both been used extensively in similar transformations[6a,7] but gave poor enantioselectivities for our system. To our delight, **L3**,[6a] developed in our group and used in other challenging transformations,[8e,11-13] was found to give the best yield/ee combination and is easily prepared. Investigation of different counterions (BF_4, SbF_6, OTf, PF_6, ClO_4) indicated that NTf_2 gave superior yields and enantioselectivity. Previous experiments in the group showed that using dichloromethane as a solvent was often beneficial. The use of a chlorinated cosolvent gave better enantioselectivity but lower yields. With hydrocarbon or ethereal cosolvents, higher yields but lower ee's were observed.

Upon scale-up (to 3 mmol of **6**) the reaction performed better, and the product could be obtained in 96% yield and 88% ee. ACAs of alkylzirconium nucleophiles often work better when scaled up; this effect is attributed to the fact that it is easier to measure and mix the reaction components at larger scales, and larger scales minimize the impact of trace air and moisture.

Having demonstrated that **9** could reliably be added to **6**, we next turned our attention to the preparation of a suitable intermediate for the synthesis of the desired product. The trapping of zirconium enolates is a challenging problem,[14] and we recently reported trapping reactions using the Vilsmeier-Haack reagent to give β-chloroaldehydes from our ACA zirconium enolates.[15] It was found that this trapping protocol also worked for our substrate; using 16.5 mmol of **6**, 3.6 grams of **11** (corresponding to 69% yield) could be obtained in 92% *ee* requiring minimal modification (see supporting information for optimization) (Scheme 3, steps a-b).

Scheme 3. Completion of the Synthesis



a) Cp_2ZrHCl (1.9 eq), CuCl/*L*3 (0.08 eq), DCE/CH_2Cl_2 rt 17 hrs; then $POCl_3$/DMF (10 eq), DCE 60 °C 1 h, 69%, 92% *ee*; b) vinylmagnesium bromide (1.2 eq), Et_2O 0 °C 1 h, 87%; c) isopropenylboronic acid pinacol ester (1.1 eq), $PdCl_2(PPh_3)_2$/dppf (0.10 eq), K_3PO_4 (3.0 eq), DMF 65 °C 17 h, 59%; d) Dess-Martin periodinane (1.2 eq), H_2O (0.50 eq), CH_2Cl_2 rt 30 min *undesired*:*desired* = 1:10, 90%; e) $TiCl_4$ (1.1 eq) slow addition, CH_2Cl_2 –35 ºC 6 h, 35%, 1:1 d.r 92% *ee*,. *Abbreviations: DCE = 1,2-dichloroethane, dppf = 1,1'-Bis(diphenylphosphino)ferrocene*.

To complete the synthesis, allylic alcohol **12** was obtained from 1,2-addition of vinylmagnesium bromide to **11**. Then, standard Suzuki-Miyaura conditions with isopropenyl boronic acid pinacol ester gave triene **13** in 59% yield.[16] The final two steps of the synthesis proved to be problematic. Triene **13** was found to be unstable under various oxidation conditions (see supporting information). Eventually, it was found that the use of Dess-Martin periodinane with one equivalent of water gave good results. Without water an allylic transposition product was observed in appreciable quantities.[17]

For the Diels-Alder reaction, we investigated a number of different conditions spanning both thermal and Lewis acid promoted transformations (see supporting information). Although the conditions reported by Baran and co-workers (3.65 eq. $BF_3{\cdot}Et_2O$, slow addition at 0 °C)[2a] gave trace product (10%

yield, 1:1 d.r., 92% ee) our substrate – being structurally different to that employed by Baran and co-workers – required extensive screening in order to reach an acceptable yield. The best results were obtained via slow addition of the substrate to a dilute and cold (–35 °C) solution of the Lewis acid which furnished **15** in 35% yield as a 1:1 mixture of diastereomers at C1 and 92% ee.

One might assume that quaternary stereocenter C8 is responsible for stereoinduction at C1 and that poor diastereoselectivity is a result of the remoteness of C8. In the Diels-Alder reaction to form **2**, Baran and co-workers observed a diastereomeric ratio of 2:1 (desired:undesired) at C3 in the cyclisation precursor which corresponded to an identical ratio at C1 in the product.[2a] While these centers are α to carbonyls, this may suggest that C3 is responsible for the diastereoselectivity, and we note that **14** lacks a C3 stereocenter.

In conclusion, the Taxol core was prepared in five steps from commercially available 3-methyl-2-cyclohex-2-ene-1-one **6** in 11% yield and 92% ee. The key step employed a hydrometallation ACA/trapping sequence of functionalized alkene **9** to furnish unsaturated β-chloroaldehyde **11** in high enantiomeric excess. Further elaboration of this intermediate to the ketone was accomplished via an addition, cross coupling and oxidation sequence. Finally, an intramolecular Diels-Alder reaction simultaneously formed the A and B rings to deliver the Taxol core. We believe that this work highlights the benefits of using organozirconium nucleophiles in asymmetric addition reactions for total synthesis and related applications.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

All procedures, characterization data, NMR spectra, and chromatography traces (PDF).

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Notes

The authors declare no competing financial interests.

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