Asymmetric Catalysis

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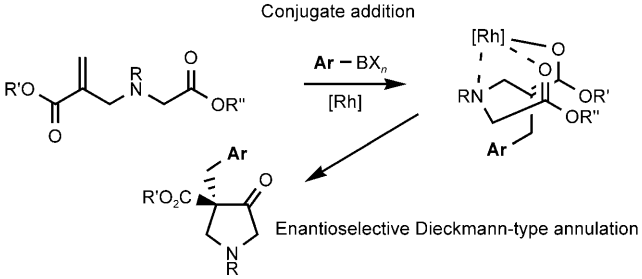
Catalytic Enantioselective Dieckmann-Type Annulation: Synthesis of Pyrrolidines with Quaternary Stereogenic Centers**

*Jonathan D. Hargrave, Joseph C. Allen, Gabriele Kociok-Köhn, Gerwyn Bish, and Christopher G. Frost**

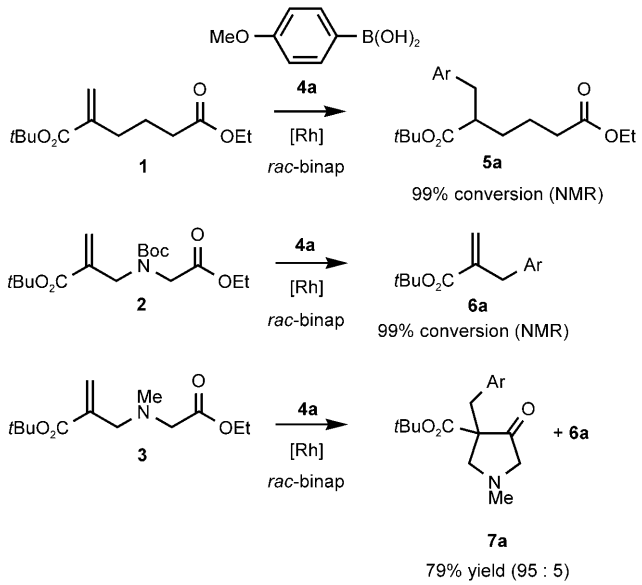
The stereoselective construction of all-carbon quaternary stereogenic centers by catalytic methodology is a highly desirable but challenging goal for synthetic chemists.[1] One approach that has met with some degree of success is the catalytic enantioselective conjugate addition of alkyl organometallic reagents to β,β′-disubstituted alkene acceptors.[2] The complementary rhodium-catalyzed enantioselective addition of aryl boronic acids[3] has also been demonstrated to be effective in establishing quaternary stereogenic centers, although reports are similarly scarce.[4] Tandem or domino catalytic reactions have emerged as valuable tools for efficient organic synthesis, including enantioselective processes.[5] In this context, Krische and co-workers reported an elegant desymmetrization approach triggered by an enantioselective conjugate addition to reveal a quaternary stereogenic center.[6] Herein, we report the development of a catalytic enantioselective Dieckmann-type annulation to form pyrrolidines with quaternary stereogenic centers.

The Dieckmann condensation offers a simple and effective method for the formation of carbon–carbon bonds in organic synthesis.[7] Examples of enantioselective Dieckmann-type annulations are surprisingly limited to desymmetrization processes that require two equivalents of a chiral leaving group.[8] Our approach involves the intramolecular reaction of a rhodium enolate with an ester to sequentially install an aryl group and a ketone across an activated alkene with the concomitant formation a quaternary stereogenic center (Scheme 1).[9] The principal challenge in the asymmetric process is that the enantioselectivity is determined at the acylation step and not, as is common in enantioselective conjugate addition reactions, at the insertion step. This reaction is similar in concept to the previously reported domino catalytic conjugate addition–enantioselective protonation of 1,1′-alkenes.[10] We anticipated that the incorporation of a hemilabile coordination site within the substrate would stabilize a reactive intermediate in a suitable conformation for cyclization. To explore the feasibility of this strategy, we examined the addition of 4-methoxyphenylboronic acid (**4a**) to substrates **1**–**3** in the presence of [{RhCl(C$_2$H$_4$)$_2$}$_2$] and *rac*-binap without an added proton source (Scheme 2).



Scheme 1. Catalytic, enantioselective synthesis of pyrrolidines with quaternary stereogenic centers.

In initial experiments, the reactions of **1** and **2** afforded none of the desired cyclized product. In the absence of a nitrogen linker, quantitative conversion into the conjugate-addition product **5a** was observed. The incorporation of the *N*-Boc functionality led to complete conversion into the α-benzyl acrylate **6a**. Interestingly, under the same conditions, the *N*-methyl analogue **3** was converted into the cyclized



Scheme 2. Domino catalytic conjugate addition–Dieckmann annulation. Reaction conditions: [{Rh(ethylene)$_2$Cl}$_2$] (2.5 mol%), *rac*-binap (5.5 mol%), **4a**, KOH, THF, 67°C. Boc = *tert*-butoxycarbonyl.

[*] Dr. J. D. Hargrave, J. C. Allen, Dr. G. Kociok-Köhn, Dr. C. G. Frost
Department of Chemistry, University of Bath
Claverton Down, Bath, BA2 7AY (UK)
Fax: (+44) 1225-386-231
E-mail: c.g.frost@bath.ac.uk
G. Bish
Pfizer Limited
Ramsgate Road, Sandwich, Kent, CT13 9NJ (UK)

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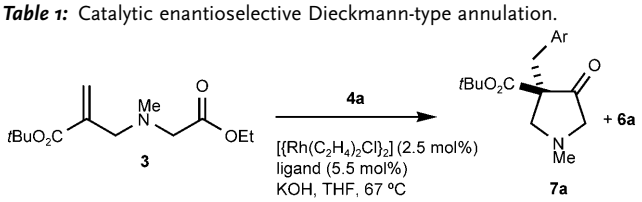
product **7a** in high yield, with only trace amounts of **6a** observed by ^{1}H NMR spectroscopy of the crude reaction mixture. These results supported our initial hypothesis and provided preliminary mechanistic insight into the stereoelectronic influence of the N linker.

Having developed a successful racemic synthesis, we next explored the asymmetric process with an enantiomerically pure ligand to access pyrrolidines with quaternary stereogenic centers (Table 1). Pleasingly, the application of enantiomerically pure binap-type bisphosphine ligands afforded **7a** as the major product with good enantioselectivity (Table 1, entries 1–5). In terms of enantioselectivity, the most advantageous ligand proved to be (*R*)-difluorphos (Scheme 3).[11] Thus, a rhodium complex generated from $[\{RhCl(C_2H_4)_2\}_2]$ (5 mol% Rh) and (*R*)-difluorphos (1.1 equiv with respect to Rh) catalyzed the reaction in THF at 67 °C to afford the cyclized product **7a** with 96% *ee* (Table 1, entry 5). The amount of elimination product **6a** observed depended on the ligand structure and reaction temperature. A striking switch to the formation of **6a** as the major (only) product was observed when the reaction was carried out at 140 °C (Table 1, entry 10) and with the chiral bicyclo[2.2.2]octadiene (dolefin) ligand (Table 1, entry 7).[12] In the latter case, the increase in the rate of β elimination over cyclization could be attributed to the increased Lewis acidity of the rhodium(I)–diene complex relative to a rhodium(I)–bisphosphine complex.[13]

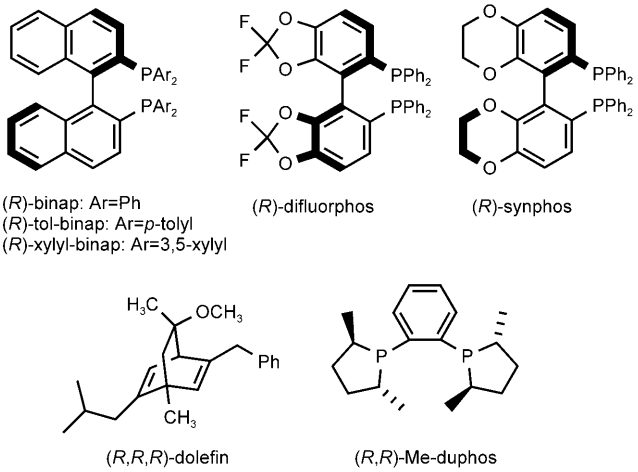
We next examined the scope of this transformation with respect to the boronic acid with both **3** and the *N*-benzyl analogue **8** (Table 2). Higher enantioselectivities were observed with difluorphos (for **3**) and synphos (for **8**) than with the other enantiomerically pure ligands. The yield and enantioselectivity of the reaction were consistently good for a range of boronic acids; however, the more sterically hindered substrate **8** afforded products with slightly lower enantioselectivity. The catalytic system tolerated a range of substituents and substitution patterns. Compound **9e** proved to be crystalline, and recrystallization resulted in an enhancement of enantiomeric purity (e.r. > 99 : < 1). The absolute configuration of **9e** was determined to be *S* by X-ray crystallography (Figure 1).[14]

Table 1: Catalytic enantioselective Dieckmann-type annulation.



Entry	Ligand	Conversion [%][a]	**7a**/**6a**[b]	e.r.[c]
1	(*R*)-binap	> 99	95:5	92:8
2	(*R*)-xylyl-binap	> 99	100:0	93:7
3	(*R*)-tol-binap	62	87:13	92:8
4	(*R*)-synphos	89	93:7	96:4
5	(*R*)-difluorphos	> 99	90:10	98:2
6	(*R*,*R*)-Me-duphos	> 99	100:0	67:33
7[d]	(*R*,*R*,*R*)-dolefin	> 99	0:100	–
8	(*S*)-binap	> 99	95:5	8:92
9[e]	(*S*)-binap	0	–	–
10[f]	(*S*)-binap	> 99	0:100	–

[a] The extent of the conversion of substrate **3** into compounds **7a** and **6a** was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] The ratio **7a**/**6a** was determined by ^{1}H NMR spectroscopy of the crude product after workup. [c] The enantiomeric ratio was determined by HPLC analysis on a chiral phase (Chiracel OD-H, 2% *i*PrOH/hexane, 0.5 mL min^{-1}). [d] The product of a second conjugate addition was isolated. [e] Reactions were carried out at 40 °C. [f] Reactions were carried out at 140 °C.



Scheme 3. Selected ligands used in the optimization of enantioselectivity.

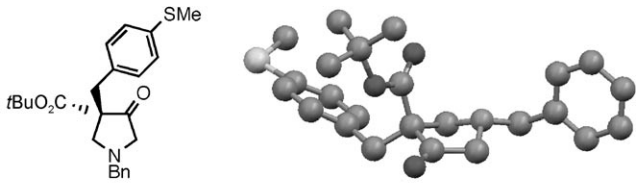
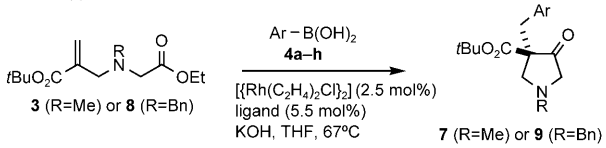


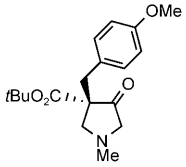
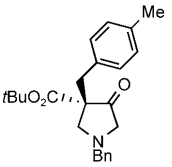
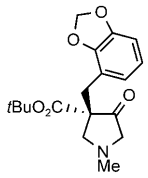
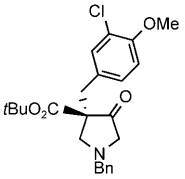
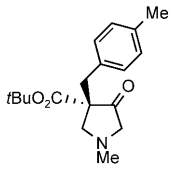
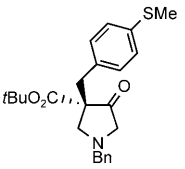
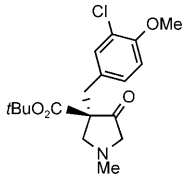
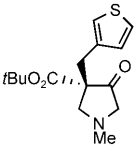
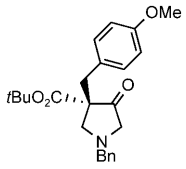
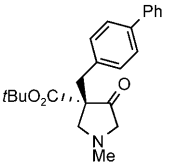
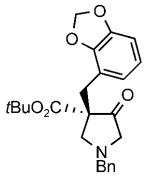
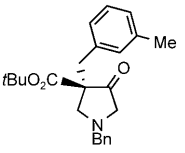
Figure 1. X-ray crystal structure of **9e**.

The efficacy of this method for the synthesis of pyrrolidines with quaternary stereogenic centers encouraged us to examine other substrates. However, our attempts to carry out an enantioselective Dieckmann-type condensation to afford piperidines were unsuccessful. The addition of 4-methylphenylboronic acid (**4c**) to substrate **10** in the presence of $[\{RhCl(C_2H_4)_2\}_2]$ and *rac*-binap resulted in the formation of conjugate-addition product **12**; the cyclization product **11** was not observed (Scheme 4). In this case, the Dieckmann pathway is disfavored as a result of the increased conformational flexibility of the substrate, and protonation of the rhodium enolate prevails.

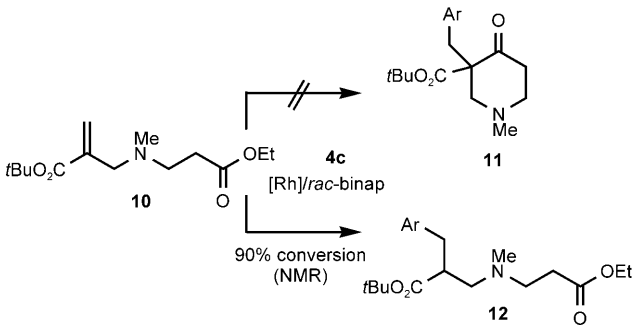
A mechanism that is consistent with the presented experimental observations is shown in Scheme 5.[15] The first step is transmetalation of the aryl boronic acid to the active rhodium complex **I** and association of the substrate to afford **II**. Subsequent carbometalation of the activated alkene gives

Table 2: Catalytic enantioselective Dieckmann-type annulation.[a]



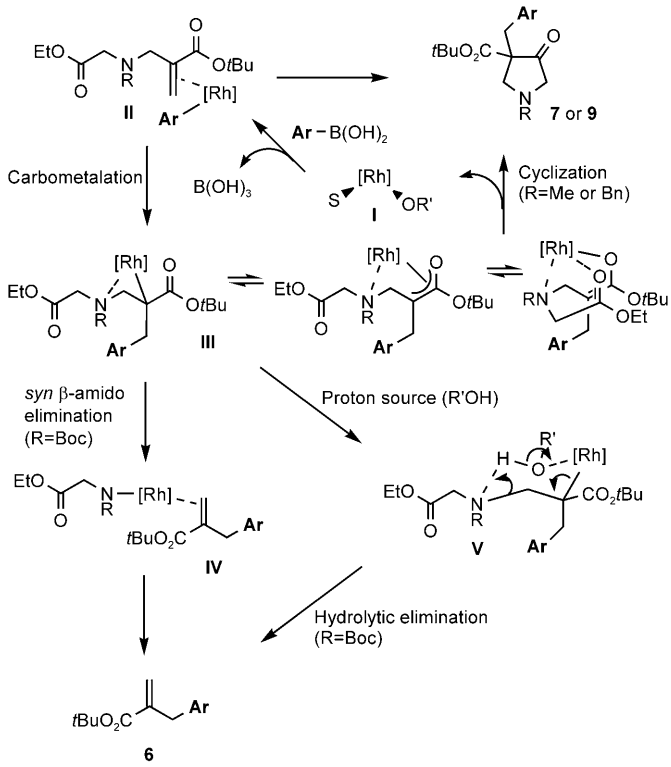
R	Ar	Product	Yield [%]	e.r.	R	Ar	Product	Yield [%]	e.r.
Me	4-$MeOC_6H_4$		**7a** 69	98:2[b]	Bn	4-MeC_6H_4		**9c** 62	93:7[d]
Me	2,3-$(OCH_2O)C_6H_3$		**7b** 63	97:3[b]	Bn	3-Cl-4-$OMeC_6H_3$		**9d** 59	92:8[e]
Me	4-MeC_6H_4		**7c** 58	94:6[b]	Bn	4-$MeSC_6H_4$		**9e** 52	92:8[d]
Me	3-Cl-4-$OMeC_6H_3$		**7d** 49	93:7[c]	Me	3-thienyl		**7f** 40	94:6[b]
Bn	4-$MeOC_6H_4$		**9a** 68	89:11[d]	Me	4-biphenyl		**7g** 60	95:5[b]
Bn	2,3-$(OCH_2O)C_6H_3$		**9b** 54	90:10[d]	Bn	3-MeC_6H_4		**9h** 58	91:9[e]

[a] See the Supporting Information for detailed experimental procedures. [b] (*R*)-Difluorphos was used as the ligand. [c] (*S*)-Difluorphos was used as the ligand. [d] (*R*)-Synphos was used as the ligand. [e] (*S*)-Synphos was used as the ligand. Bn = benzyl.



Scheme 4. Attempted catalytic synthesis of piperidines with quaternary stereogenic centers. Reaction conditions: [{$Rh(C_2H_4)_2Cl$}$_2$] (2.5 mol%), *rac*-binap (5.5 mol%), **4c**, KOH, THF, 80°C.

an η^1-C rhodium species **III**,[10f] which is anticipated to be in equilibrium with an oxa-π-allyl species[15] or η^1-O rhodium enolate.[16] The presence of a coordinating functionality in the substrate at the β position induces competition between cyclization and elimination pathways. The combination of an NMe linker and a diphosphine ligand results in cyclization to afford **7**, presumably via the η^1-O haptomer. Similarly, the presence of the NBn linker facilitates cyclization to afford **9**. The treatment of substrate **3** with [{$RhCl(C_2H_4)_2$}$_2$], KOH, and *rac*-binap in the absence of an aryl boronic acid resulted in no change in the ^{1}H NMR spectrum of **3**, which suggests that no elimination occurs prior to C–C bond formation. Interestingly, we observed no formation of the elimination



Scheme 5. Mechanistic proposal for the formation of the cyclization and elimination products.

product **6a** when the product **7a** was reexposed to the reaction conditions. The experimental evidence suggests a competitive catalytic pathway. The α-benzyl acrylate **6** could arise from the η^1-C rhodium species **III** through a *syn* β-amido elimination pathway to afford **IV** in a process reminiscent of the elimination step proposed by Darses and co-workers for the rhodium-catalyzed reaction of unactivated Baylis–Hillman adducts with aryl boronic acids.[17] Alternatively, a hydrolytic elimination pathway via **V** that involves the coordination of a proton source to a η^1-C rhodium intermediate is postulated.[18] The dominant pathway appears to be dictated by a ligand-dependent equilibration between rhodium enolate species. The enhanced Lewis acidity of the rhodium(I)–diene complex relative to a rhodium(I)–bisphosphine complex would be expected to lead to an increase in the rate of β elimination by either of the presented pathways. Further investigations into the mechanism of this reaction and the striking ligand effects are ongoing in our laboratories.

In conclusion, we have established a new method to form pyrrolidines with quaternary stereogenic centers through a catalytic enantioselective Dieckmann-type annulation. The presence of an amine coordination site within the substrate was necessary to stabilize a reactive intermediate in a suitable conformation for cyclization. The asymmetric process is triggered by the addition of an aryl boronic acid; however, crucially, the enantioselectivity is determined at the acylation step and not, as is common in enantioselective conjugate addition reactions, at the insertion step. This method of catalytic acylation is of significant potential utility in enantioselective synthesis, and further applications are anticipated.

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[18] The proton source could be boric acid, ethanol, or adventitious water produced through condensation processes involving the boronic acid.

