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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2079–2082

Synthesis of C_2-symmetric *trans*-2,6-diarylpiperidinones via aryl cuprate addition: an unexpected stereochemical outcome

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Received 22 December 2006; revised 17 January 2007; accepted 25 January 2007
Available online 30 January 2007

Abstract—An efficient procedure for the preparation of *trans*-2,6-diaryl piperidinones has been developed. Addition of aryl Grignard reagents to 2-aryl dihydropyridones under catalytic copper promoted conditions generates the trans isomer exclusively, an unprecedented stereochemical event. The X-ray structures of both starting material and product have been solved and shed light on the steric constraints and substrate geometry leading to the observed product. The reaction conditions tolerate a variety of aromatic nucleophiles to generate C_2-symmetric products in good overall yields.

The utility of substituted piperidinones as organic building blocks has driven the development of a variety of methodologies aimed at the synthesis of a diverse array of analogues.[1] In particular, the utilization of *N*-acyl-2,3-dihydro-4-pyridones as synthetic precursors is well documented by Comins et al. (Fig. 1).[2]

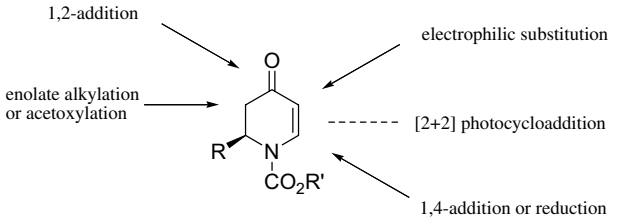
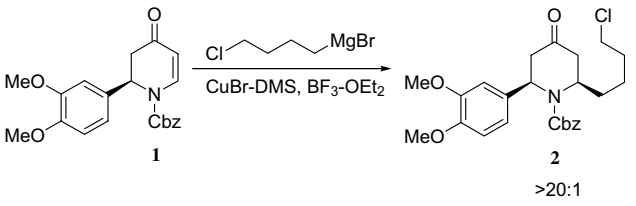
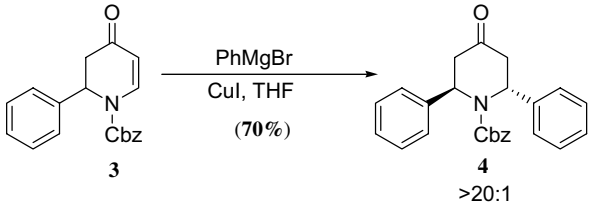


Figure 1. General utility of 2,3-dihydro-4-pyridones.

Examples of conjugate Grignard additions under copper promoted conditions have been reported to give the *cis* 2,6-disubstituted piperidinones in good yield and selectivity, Eq. 1.[2b] Extension of this methodology to generate 2,6-diarylpiperidinones has not previously been disclosed to our knowledge. Subjection of 2-phenyl-3,4-dihydro-4-pyridone (**3**) to copper-catalyzed conjugate addition[2a] conditions proceeded smoothly to give diaryl piperidinone **4** in excellent yield, Eq. 2. To our surprise,



(1)



(2)

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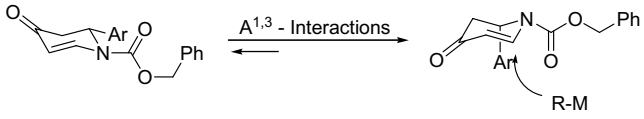
doi:10.1016/j.tetlet.2007.01.135

further examination of the product by NMR revealed that the *trans*-2,6-diphenyl piperidinone was formed exclusively, an unprecedented stereochemical outcome.

Comins and co-workers has proposed that the high cis-stereoselectivity[1c,2a,b] in the synthesis of **2** arises from stereoelectronically preferred axial attack[3] of the cuprate reagent via a chair-like transition state where the existing aryl substituent lies pseudoaxial to avoid $A^{1,3}$-interactions[4] with the sterically sizable *N*-CBz group.



In order to fully understand the reactivity of the unsaturated piperidinone **3**, a high quality X-ray crystal structure was solved (Fig. 2). This structure reveals that the compound exists in a half boat conformation, which is set up for axial delivery opposite the face of the existing phenyl group providing the observed trans product. This model accounts for both steric and electronic factors favoring observed product and is consistent with extensive solution NMR studies.[5]

A crystal structure of product piperidinone **4** was also solved (Fig. 3). This structure adopts a twist boat type conformation alleviating both $A^{1,3}$-strain and diaxial interactions that would be present in a chair conformation. Inference from both crystal structures favors a model wherein the transition state adopts a pseudo twist boat conformation to alleviate all steric interactions and to allow for stereoelectronically preferred axial bond formation.

A number of conditions were explored for this aryl cuprate addition (Table 1). In the absence of a copper catalyst the reaction did proceed but in low yield (entry 1). In the presence of a copper source, such as CuI, CuCN, or CuBr·SMe_2, aryl addition also gave exclusively *trans*-piperidinone **4**, but in improved yields. The general applicability of this reaction using a variety of copper

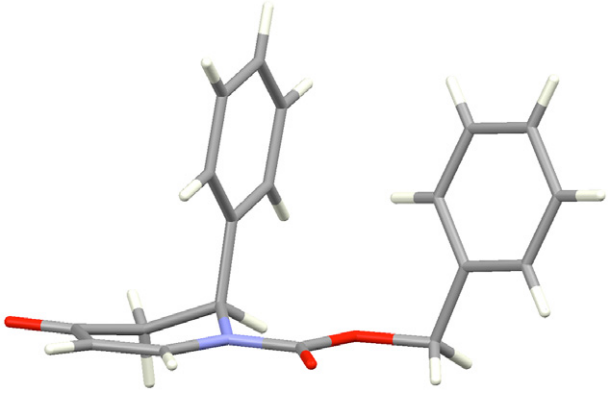


Figure 2. X-ray structure of **3**.

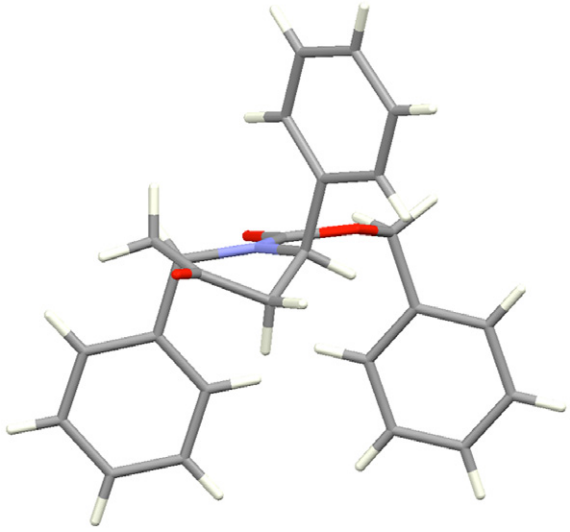
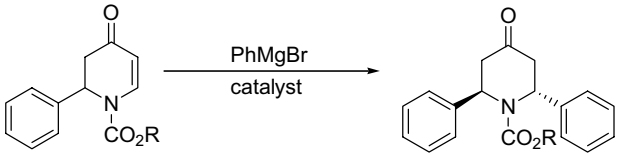


Figure 3. X-ray structure of **4**.

Table 1. Control experiments



3 **4**

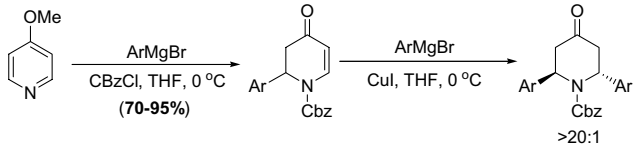
Entry	Catalyst	Solvent	R	Yield (%)	Trans:cis
1	None	THF	Bn	26	>20:1
2	CuI	THF	Bn	70	>20:1
3	CUCN CuBr–DMS	THF	Bn	68	>20:1
4	BF_3–OEt_2[a]	THF	Bn	68	>20:1
5	CuI	1,4-Dioxane	Bn	<5	NA
6	CuI	DME	Bn	<5	NA
7	CuI	THF	Et	76	>20:1
8	CuI	THF	$C(CH_3)_2CCl_3$	61[b]	>20:1

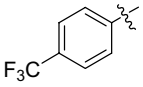
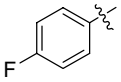
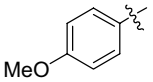
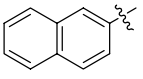
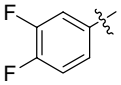
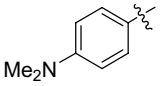
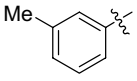
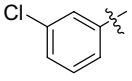
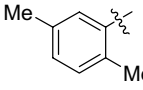
[a] Excess reagent employed (CuBr–DMS, 3 equiv; BF_3–OEt_2, 16 equiv).
[b] Excess catalyst employed (1.75 equiv).

sources indicates that subtle changes in aryl cuprate aggregation state likely have little influence on either the yield or selectivity of the reaction.[6] Choice of solvent is critical for the success of the reaction and the highest yields are achieved when the reaction is performed in THF. It is important to note that the reaction afforded piperidinone **4** in very low yield when performed in DME or 1,4-dioxane (entries 5 and 6).

To investigate the role of the *N*-acyl group on the stereochemical outcome of the aryl addition, we prepared a variety of *N*-acyl derivatives. Both ethyl carbamate (entry 7) and benzyl carbamate (entry 2) gave exclusively the trans addition products, which suggest that a π-stacking[7] assembly in the transition state between the phenyl group of the carbamate and the existing phenyl group of the piperidinone likely does not play a role for delivery of the phenyl cuprate reagent. The fact that the sterically large trichloro-Boc group also leads to the *trans*-piperidinone and none of the cis product suggests that the sterics of the *N*-acyl group play a very limited role in the stereochemical outcome of the aryl addition.

Table 2. Substrate scope for the aryl conjugate addition[a]

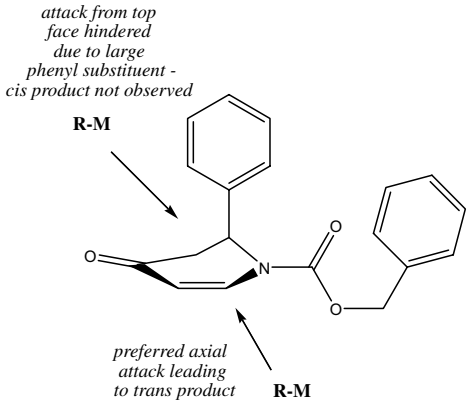


Entry	Ar	Yield (%)
1		70
2		56
3		72
4		74
5		44
6		33
7		46
8		47
9		59
10[b]		46

[a] Reaction conditions: 1.75 equiv ArMgBr, 0.2 equiv CuI.
[b] Modification: the reaction was performed at 4 °C overnight.

Given the potential utility of C_2-symmetric piperidinones further investigations were initiated. The substrate scope of this aryl conjugate addition was examined (Table 2).[8] Both electron-rich (entry 4) and electron poor (entry 2) aryl cuprates were tolerated and in all cases provided exclusively the *trans*-2,6-diarylpiperidinone. Sterically demanding aryl cuprates such as napthyl, 2,5-dimethyl (entries 5 and 10, respectively) gave product in good overall yields. In addition, the use of halogen and heteroatom substituents extends the scope of this methodology (entries 2–4, 6, 7, 9).

In summary, we have discovered an unprecedented stereospecific aryl cuprate addition to 2-aryl dihydropyridones. C_2-symmetric piperidinones bearing aryl substituents may be valuable both as intermediates for ligands/catalysts employed in asymmetric transformations and as versatile synthetic precursors. The scope of the efficient trans cuprate addition described herein allows for expeditious and variable tuning of the ligand/catalyst design. To that end, studies aimed at extension of this methodology to enantioselective preparations[9] of diaryl piperidinones are underway.



Acknowledgment

The authors would like to acknowledge Dr. Ben Munoz for helpful discussions with the development of this methodology and Grace Bi for chromatographic analysis.

Supplementary data

NMR characterization studies. Crystallographic data for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Numbers CCDC 631813 and CCDC 631814. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.135.

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8. *General procedure for the preparation of aryl piperidinones using CuI as a catalyst*: A suspension of copper iodide (62 mg, 0.33 mmol) in THF (10 mL) was cooled to 0 °C and treated with phenyl magnesium bromide (2.85 mmol, 2.85 mL of a 1 M solution) and stirred for 30 min. A solution of dihydropyridone **3** (0.5 g, 1.63 mmol) in THF (10 mL) was added to the reaction mixture at 0 °C and the resulting solution was stirred at this temperature for 2 h. The reaction mixture was quenched with ammonium chloride/ammonium hydroxide solution and partitioned between water and ethyl acetate. The organics were dried over sodium sulfate, filtered, and evaporated in vacuo. Purification by flash column chromatography (15–25% ethyl acetate/hexanes) gave 0.44 g (70%) of piperidinone **4** as a white solid.
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