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Enantioselective Arylation of 2-Methylacetoacetates Catalyzed by CuI/*trans*-4-Hydroxy-L-proline at Low Reaction Temperatures

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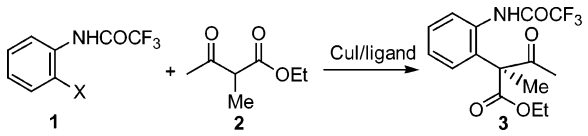
A considerable number of natural products and pharmaceutically important compounds contain α-aryl all-carbon quaternary centers. Such molecules include diazonamide,[1] physostigmine,[2] and gelsenicine-related oxindole alkaloids.[3] Enantioselective generation of this type of stereocenter is still a challenge for synthetic organic chemists.[4] Among the emerging methods,[4−8] asymmetric arylation of enolates was attractive because of the ready availability of the coupling substrates.[8] Until now this approach was only achieved by employing palladium and nickel catalysts.[8] Recently, we reported that CuI-catalyzed coupling of aryl halides with β-keto esters, assisted by L-proline, took place at 40−50 °C.[9] We envisioned that asymmetric induction by the chiral ligand L-proline might occur. However, rapid racemization occurred at the newly formed chiral center, preventing the formation of optically active products. To solve this problem, we attempted to utilize 2-alkyl acetoacetates as the coupling agents. Unfortunately, they were found to be poor substrates under our standard conditions. Later, we discovered that the $NHCOCF_3$ group in 2-halotrifluoroacetanilides can promote the Ullmann-type biaryl ether formation reaction,[10] which encouraged us to test our hypothesis by using these more reactive aryl halides.

As expected, reaction of 2-bromotrifluoroacetanilide (**1a**) with ethyl 2-methylacetoacetate, catalyzed by CuI/L-proline, took place at room temperature, providing the coupling product **3** in 43% yield, whereas approximately 50% of **1a** was recovered. To our delight, asymmetric induction was achieved, and an ee value of 37% was determined by chiral HPLC (Table 1, entry 1). Changing **1a** to 2-iodotrifluoroacetanilide (**1b**) resulted in improved yield and enantioselectivity (entry 2), indicating that iodides are more reactive than bromides, which was inconsistent with the observations made in the biaryl ether formation reaction. In addition, *trans*-4-hydroxy-L-proline was found to work in this reaction as well (entry 3).

Occasionally, when DMSO containing traces of water was used, the reaction was much faster (entry 4).[11] Thus, other solvents containing 0.5% water were examined. However, only DMF displayed an identical effect, whereas wet methylene chloride, dioxane, THF, and acetone resulted in decreased enantioselectivity (see Supporting Information) even though the coupling reactions proceeded well. Replacement of Cs_2CO_3 with NaOH had little influence on the process, and therefore the latter was chosen as the base in subsequent studies. The discovery of DMF as an alternative solvent allowed us to improve the enantioselectivity by reducing the reaction temperatures. Indeed, coupling occurred smoothly at −20, or even at −45 °C, providing **3** with increased optical purity (entries 7 and 8). *It is noteworthy that these results represent a new record low in reaction temperatures for Ullmann-type coupling reactions as only two room-temperature reactions were disclosed quite recently.*[10,12] It should encourage the further development of milder Ullmann-type coupling reactions. Interestingly, when L-proline was tested, no coupling took place at −45 °C. This illustrates that *trans*-4-hydroxy-L-proline is a superior ligand to L-proline, although the reason for this difference is not clear.

Table 1. CuI-Catalyzed Coupling Reaction of Aryl Halides **1** with Ethyl 2-Methylacetoacetate **2**[a]



entry	X	ligand[b]	base	solvent	time (h)	yield (%)[c]	ee (%)[d]
1	Br	A	Cs_2CO_3	DMSO	24	43[h]	37
2	I	A	Cs_2CO_3	DMSO	18	69	43
3	I	B	Cs_2CO_3	DMSO	24	75	44
4	I	B	Cs_2CO_3	DMSO[e]	3	87	44
5	I	B	Cs_2CO_3	DMF[e]	3	80	44
6	I	B	NaOH	DMF[e]	3	81	45
7	I	B	NaOH	DMF[e]	4	80	62[f]
8	I	B	NaOH	DMF[e]	4	80	71[g]
9	I	A	NaOH	DMF[e]	4	−[h]	−

[a] Reaction conditions: CuI (0.1 mmol), ligand (0.2 mmol), **1** (0.5 mmol), **2** (0.75 mmol), base (2 mmol), solvent (1 mL), rt. [b] A: L-proline, B: *trans*-4-hydroxy-L-proline. [c] Isolated yields. [d] Determined by chiral HPLC. [e] 5 μL of water was added. [f] Reaction was carried out at −20 °C. [g] Reaction was carried out at −45 °C. [h] About 50% halide was recovered.

With optimized ligand and reaction conditions established, further modifications were conducted by varying the β-keto esters. As summarized in Table 2, increasing the size of the ester moiety remarkably improved the enantioselectivity; this was evident from the fact that 89% ee was achieved using *tert*-butyl 2-methylacetoacetate as a substrate (compare entries 1−3). Using this β-keto ester, a variety of substituted 2-iodotrifluoroacetanilides were evaluated. It was revealed that the electronic nature of the substituents on the aryl iodides has a pronounced effect on the overall efficacy of the process. For example, substrates bearing an electron-rich substituent all gave good conversions and enantioselectivities (up to 93% ee, entries 4−7), whereas aryl iodides that possess an electron-withdrawing group required higher reaction temperatures to ensure complete conversion (entries 8, 9, and 11) or gave lower yields of cross-coupling product due to reductive homo-coupling of the corresponding aryl iodide (entry 10). A similar reactivity trend for aryl halides has been observed during our investigations on the biaryl ether formation reaction.[10] In case of 2,4-diiodotrifluoroacetanilides, only coupling product **5g** was isolated, which clearly demonstrated that an ortho substitution effect caused by the $NHCOCF_3$ group also exists in the present transformation.

To determine the absolute stereochemistry of the coupling products, the keto ester **5a** was transformed into a known oxindole

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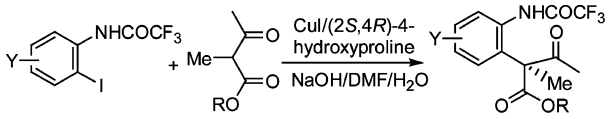
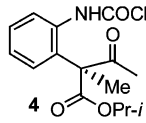
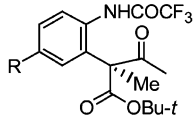
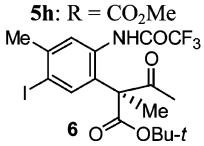
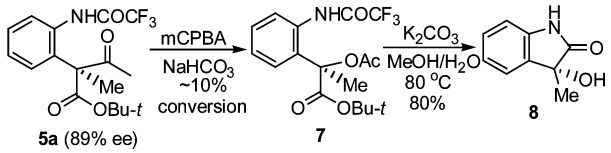
Table 2. CuI-Catalyzed Coupling of 2-Iodotrifluoroacetanilides and 2-Methylacetoacetates[a]



Entry	Product	Temp. (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**3**	-45	3	80	71
2	 **4**	-45	36	70	74
3	 **5a**: R = H	-45	30	77	89
4	**5b**: R = Me	-45	30	79[d]	93
5	**5c**: R = CH_2OH	-45	30	77[d]	91
6	**5d**: R = OMe	-45	30	78[d]	87
7	**5e**: R = $C(OCH_2)_2Me$	-45	6	82	86
8	**5f**: R = F	-30	24	81	83
9	**5g**: R = I	-20	36	79	81
10	**5h**: R = CO_2Me	-45	36	29[e]	60
11	 **6**	-20	48	72[d]	82

[a] Reaction conditions: iodide (0.5 mmol), β-keto ester (0.75 mmol), CuI (0.1 mmol), *trans*-4-hydroxy-L-proline (0.2 mmol), NaOH (2 mmol), DMF (1 mL), H_2O (5 μL). [b] Isolated yields. [c] Determined by chiral HPLC. [d] 5 mmol of NaOH was added. [e] Reductive coupling product was isolated in 22% yield.

Scheme 1. Conversion of **5a** to oxindole **8**



8[13] as depicted in Scheme 1. Baeyer−Villiger oxidation of **5a** with mCPBA under solvent-free conditions produced ester **7**, which was treated with aqueous K_2CO_3 in MeOH to afford **8**. By comparing the rotation of our synthetic **8** ($[\alpha]_D^{27}$ +46 (*c* 0.63, MeOH) with that reported for (*R*)-**8** ($[\alpha]_D^{27}$ +50 (*c* 1.0, MeOH)),[13] we concluded that the configuration of our coupling products is *S*.

In conclusion, we have found that CuI-catalyzed coupling between aryl iodides and β-keto esters can be performed at −45 °C through a combination of ortho substitution and ligand and solvent effects. This represents the lowest reaction temperature for Ullmann-type reactions so far. The excellent enantioselectivity provided evidence for the participation of the Cu(I)−amino acid chelate in the transition state of the reaction. This observation is expected to be useful for mechanistic studies of Ullmann-type reactions.[14] In addition, the inexpensive catalytic system makes this asymmetric coupling reaction valuable for organic synthesis. For example, compound **5d** may serve as an ideal intermediate to assemble physostigmine and related natural products.[2,5,15] Further exploration on the scopes and limits of the synthetic application are in progress.

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Supporting Information Available: Experimental and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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