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Synthesis of 2-alkyl-2-arylcyanoacetates via CuI/sodium picolinate-catalyzed direct arylation of α-substituted cyanoacetates

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ABSTRACT

CuI/sodium picolinate-catalyzed direct arylation of α-substituted cyanoacetates takes place at 60 °C in the presence of Cs_2CO_3 and 4 Å molecular sieve, affording 2-alkyl-2-arylcyanoacetates in good to excellent yields. Both electron-rich and electronic-deficient aryl iodides, and some functionalized α-substituted cyanoacetates are compatible with the reaction conditions, thereby allowing diverse synthesis of 2-alkyl-2-arylcyanoacetates.

Copper-mediated arylation of malonates, namely Hurtley reaction,[1] is an attractive approach for assembling α-arylated malonate derivatives that are useful precursors to nonsteroidal anti-inflammatory drugs like Ibuprofen and Naproxen.[2] The traditional reaction conditions for this transformation normally require a stoichiometric amount of copper salts as the catalysts and relatively high reaction temperatures.[3] Under these conditions, substrate scope is quite narrow and poor to moderate yields were often observed. However, the situation has been dramatically changed in recent years.[3] This is because some special ligands such as 2-phenylphenol,[4] L-prolines,[5] 2-picolinic acid,[6] and chelating Schiff bases[7] were found to be able to accelerate Hurtley-type coupling reactions. Under the assistance of these ligands, mild conditions for copper-catalyzed arylation of malonates,[4–7] ethyl cyanoacetate,[5b,7] acetylacetone,[5b] and β-keto esters[5a] have been discovered. Based on these investigations, some conceptually novel methods for heterocycle synthesis have been developed. These heterocycles include carbazoles,[8] indoles,[9] benzofurans,[10] isoquinolines,[11] 3-acyloxindoles,[12] as well as isoquinolin-1(2*H*)-ones.[13]

Although the progress in this field is remarkable, creation of a quaternary carbon center through a copper-catalyzed direct coupling reaction of aryl halides with suitable nucleophiles is still challenging. We have reported that CuI/*trans*-4-hydroxy-L-proline catalyzed arylation of 2-methyl-acetoacetates could take place by using highly reactive 2-halotrifluoroacetanilides as the coupling partners.[14] As an extension of this work, in this Letter, we explore the possibility of ligand-promoted copper-catalyzed arylation of α-substituted cyanoacetates. We found this coupling reaction worked well under the catalysis of CuI and some special ligands, thereby providing a valuable approach for synthesizing 2-alkyl-2-arylcyanoacetates. Herein, we wish to disclose our results.

In 1996, Miura et al.[15] reported that copper-catalyzed coupling of aryl iodides with ethyl 2-cyanopropanoate took place at 80 °C to afford ethyl 2-cyano-2-phenylpropionate. However, only 69% conversion could be reached even using 1.3 equiv of CuI. We envisioned that this reaction could be improved by using suitable ligands, and therefore a coupling reaction of 4-iodoanisole with ethyl 2-cyanopropanoate was conducted. It was found that under the catalysis of 10 mol % CuI and 20 mol % *trans*-hydroxy-L-proline, the reaction completed at 60 °C, affording the desired coupling product **3a** in 65% yield, together with 2-(4-methoxyphenyl)propanenitrile **4a** in 16% yield (Table 1, entry 1). Changing ligand to *trans*-hydroxy-L-proline sodium salt gave an improved result (entry 2). Considering that **4a** should be a decarboxylation product of **3a**, we decided to add 4 Å molecular sieve to inhibit the hydrolysis of **3a**. To our delight, in this case no **4a** was determined and yield of **3a** could be increased to 77% (entry 3). The best result was observed when ligand was switched to sodium picolinate (entry 4). Changing ligand to sodium piperidine-2-carboxylate gave a decreased yield (entry 5), while using other ligands like *N*,*N*′-dimethylethane-1,2-diamine, 1,10-phenanthroline, BINOL, and 8-hydroxy-quinoline did not give any coupling products (entries 6–9). Further investigations revealed that the coupling reaction is quite sensitive to both temperatures and bases, as evident from that no conversion was found at 40 °C (entry 10), and decreased yields were observed when K_2CO_3 and K_3PO_4 were

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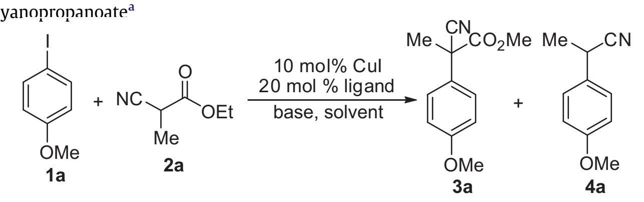
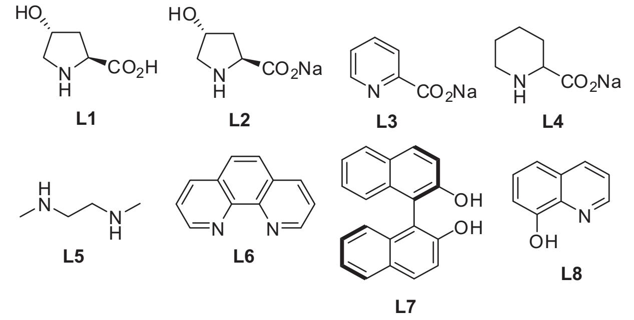
Table 1
CuI/ligand-catalyzed coupling reaction of 4-iodoanisole with ethyl 2-cyanopropanoate[a]





Entry	Ligand	Base	Solvent	Yield[b] (%)
1	**L1**	Cs_2CO_3	DMSO	65[c]
2	**L2**	Cs_2CO_3	DMSO	70[d]
3[e]	**L2**	Cs_2CO_3	DMSO	77
4[e]	**L3**	Cs_2CO_3	DMSO	89
5[e]	**L4**	Cs_2CO_3	DMSO	34
6	**L5**	Cs_2CO_3	DMSO	0
7	**L6**	Cs_2CO_3	DMSO	0
8	**L7**	Cs_2CO_3	DMSO	0
9	**L8**	Cs_2CO_3	DMSO	0
10[e,f]	**L3**	Cs_2CO_3	DMSO	0
11[e]	**L3**	K_2CO_3	DMSO	65
12[e]	**L3**	K_3PO_4	DMSO	67
13[e]	**L3**	Cs_2CO_3	DMF	80
14[e]	**L3**	Cs_2CO_3	1,4-Dixoane	0

[a] Reaction conditions: 4-iodoanisole (0.5 mmol), ethyl 2-cyanopropanoate (1.5 mmol), CuI (0.05 mmol), ligand (0.1 mmol), Cs_2CO_3 (1.5 mmol), DMSO (1.5 mL), 60 °C, 24 h.

[b] Isolated yield.

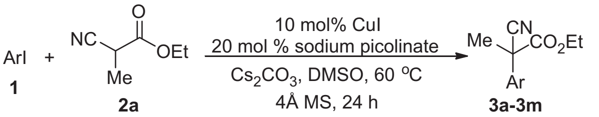
[c] **4a** was isolated in 16% yield.

[d] **4a** was isolated in 10% yield.

[e] 0.3 g of 4 Å MS was added.

[f] Reaction was carried out at 40 °C.

Table 2
CuI/sodium picolinate-catalyzed arylation of ethyl 2-cyanopropanoate[a]



Entry	Ar	Product	Yield[b] (%)
1	$4\text{-}MeC_6H_4$	**3b**	85
2	$4\text{-}FC_6H_4$	**3c**	89
3	$4\text{-}ClC_6H_4$	**3d**	83
4	$4\text{-}AcNHC_6H_4$	**3e**	73
5[c]	$4\text{-}NO_2C_6H_4$	**3f**	90
6	$3\text{-}MeC_6H_4$	**3g**	88
7	$3\text{-}MeOC_6H_4$	**3h**	85
8	$3\text{-}FC_6H_4$	**3i**	86
9	$3,5\text{-}Me_2C_6H_3$	**3j**	76
10[d]	$2\text{-}MeOC_6H_4$	**3k**	39
11	2-Pyridinyl	**3l**	87
12	2-Naphthyl	**3m**	80

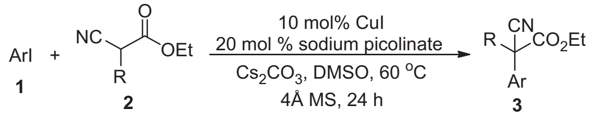
[a] Reaction conditions: aryl iodide (0.5 mmol), ethyl 2-cyanopropanoate (1.5 mmol), CuI (0.05 mmol), sodium picolinate (0.1 mmol), Cs_2CO_3 (1.5 mmol), 4 Å MS (0.3 g), DMSO (1.5 mL), 60 °C, 24 h.

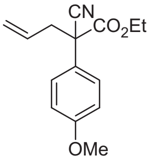
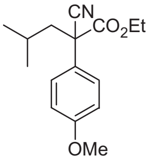
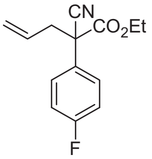
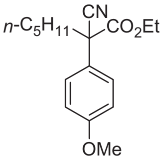
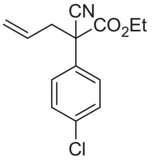
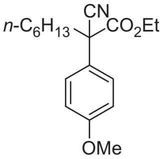
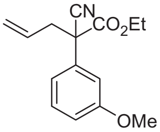
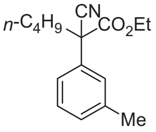
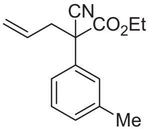
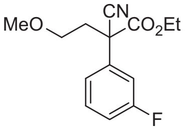
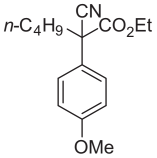
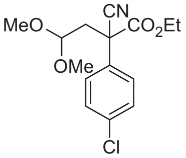
[b] Isolated yield.

[c] Reaction was carried out at 40 °C.

[d] Reaction time was 36 h.

Table 3
CuI/sodium picolinate-catalyzed arylation of α-substituted 2-cyanopropanoates[a]



Entry	Product yield[b] (%)	Entry	Product yield[b] (%)
1	 **3n** (82%)	7	 **3t** (71%)
2	 **3o** (80%)	8	 **3u** (79%)
3	 **3p** (84%)	9	 **3v** (78%)
4	 **3q** (81%)	10	 **3w** (80%)
5	 **3r** (86%)	11	 **3x** (84%)
6	 **3s** (84%)	12	 **3y** (77%)

[a] Reaction conditions: aryl iodide (0.5 mmol), ethyl 2-cyanopropanoate (1.5 mmol), CuI (0.05 mmol), sodium picolinate (0.1 mmol), Cs_2CO_3 (1.5 mmol), 4 Å MS (0.3 g), DMSO (1.5 mL), 60 °C, 24 h.

[b] Isolated yield.

employed as the bases (entries 11 and 12). Solvent is another important factor to influence the reaction course because a decreased yield was obtained in DMF (entry 13) and no conversion was observed in dioxane (entry 14).

Since enantiopure ligands such as **L1** and **L2** were used and a chiral quaternary carbon center was generated in the present coupling reaction, we wondered if some enantioselectivity could be achieved and therefore the enantiopurity of **3a** was measured. Disappointingly, ee value of **3a** was close to zero, which meant that there was no asymmetric induction during the reaction course.

More explorations are required to reach good enantioselectivity by using other enantiopure ligands.

Having the optimized reaction conditions in hand, we examined a number of substituted aryl iodides to explore the reaction scope and limitations. As summarized in Table 2, coupling reactions of ethyl 2-cyanopropanoate with both electron-rich and electron-deficient aryl iodides completed smoothly under these conditions, providing the corresponding arylation products in 73–90% yields. The coupling reaction of 4-nitroiodobenzene even took place at 40 °C (entry 5). The only exception came from one *ortho*-substituted aryl iodide, which led to poor conversion even after prolonging reaction time (entry 10). This result indicated that steric hindrance of aryl iodides could greatly decrease the coupling rate.

We next examined the reaction scope by varying α-substituted ethyl 2-cyanoacetates. Gratifyingly, coupling reaction of ethyl 2-cyanopent-4-enoate with several aryl iodides proceeded well under the optimized conditions to deliver **3n**–**r** in good yields (Table 3, entries 1–5). Elongation of the side chain of α-substituted ethyl 2-cyanoacetates has little influence on the reaction, as evident from that **3s**–**w** were obtained in similar reaction yields (entries 6–10). Additionally, two functionalized α-substituted ethyl 2-cyanoacetates were compatible with these conditions, leading to formation of **3x** and **3y**.

In summary, we have demonstrated that combination of CuI and sodium picolinate is a powerful catalytic system for promoting direct arylation of α-substituted cyanoacetates. Our result not only extends the scope of ligand-promoted Ullmann-type coupling reactions, but also provides a reliable method for preparing synthetically important 2-alkyl-2-arylcyanacetates.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.057.

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