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Enantioselective Construction of Quaternary All-Carbon Centers via Copper-Catalyzed Arylation of Tertiary Carbon-Centered Radicals

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Supporting Information

ABSTRACT: An enantioselective copper-catalyzed arylation of tertiary carbon-centered radicals, leading to quaternary all-carbon stereocenters, has been developed herein. The tertiary carbon-centered radicals, including both benzylic and non-benzylic radicals, were produced by the addition of trifluoromethyl radical to α -substituted acrylamides, and subsequently captured by chiral aryl copper(II) species to give C-Ar bonds with excellent enantioselectivity. Importantly, an acylamidyl (CONHAr) group adjacent to the tertiary carbon radical is essential for the asymmetric radical coupling. The reaction itself features broad substrate scope, excellent functional group compatibility and mild conditions.

Owing to the prevalence of optically pure quaternary allcarbon centers in natural products and bioactive compounds,¹ the catalytic asymmetric synthesis of molecules bearing quaternary all-carbon stereocenters has been considered as an important goal in modern organic synthesis.² Therefore, considerable effort has been directed toward the straightforward and efficient construction of the highly congested quaternary all-carbon stereocenters, such as asymmetric cycloadditions, allylic substitutions, Heck reactions and so on.² In the last decades, radical-based metal-catalyzed cross coupling has been regarded as a powerful tool for the formation of C-C bonds,³ including coupling reactions of tertiary carbon-centered radicals.⁴

Although the asymmetric coupling of secondary carboncentered radicals has been successfully achieved by introducing chiral ligands,³ the asymmetric coupling of tertiary carboncentered radicals still remains a formidable challenge in asymmetric radical transformations (ARTs). Very recently, Fu and coworkers reported an elegant enantioconvergent coupling of tertiary electrophiles with olefins for the formation of chiral quaternary all-carbon centers, which involves the asymmetric coupling of the tertiary carbon-centered radicals with chiral (Box)Ni^{II}-alkyl species.⁵

As part of our continuous research program to develop asymmetric radical transformations (ARTs),⁶ a series of enantioselective functionalizations of alkenes⁷ and benzylic C-H bonds,⁸ such as cyanation,^{7a-b,8a} arylation^{7d-e} and alkynylation^{7f}, have been developed via a copper-catalyzed radical relay process. In these reactions, a benzylic radical (R = H) as a key intermediate was enantioselectively captured by reactive chiral L*Cu^{II}-FG species (FG = CN, Ar and alkynyl) to forge enantiomerically enriched C-C bonds (Scheme 1A, left).^{7,8a,9} Nevertheless, these asymmetric transformations are limited to the reaction of secondary benzylic radicals, the enantioselective trapping of nonbenzylic and tertiary carbon-centered radicals is still unsuccessful. Herein, we communicate an asymmetric copper-catalyzed trifluoromethyl-arylation of α -substituted acrylamides, providing a straightforward and efficient access to chiral quaternary allcarbon centers, wherein both benzylic and non-benzylic tertiary carbon-centered radicals can be enantioselectively trapped by L*Cu^{II}Ar species (Scheme 1B).



Scheme 1. Asymmetric radical transformations via Cu-catalyzed radical relay. RA: radical addition, HAT: hydrogen atom transfer.

Based on our previously reported asymmetric arylation of styrenes,^{7d} we turned our attention to investigating the arylation of tertiary carbon-centered producing chiral quaternary all-carbon centers. Unfortunately, the reactions of α -methylstyrene failed to deliver the arylation products (Scheme 1A, right). The reasons might account for the tertiary benzylic radical (R = Me) as following: (1) the increased steric repulsion between the bulky tertiary benzylic radical and chiral (L*)Cu^{II}Ar species impedes their interaction; or (2) the weaker oxidative ability of the tertiary benzylic radical makes the oxidation of (L*)Cu^{II}Ar unfavorable.¹⁰ Inspired by the pioneering study of Peters and Fu,¹¹ we envisaged

that introducing a carbonyl group instead of the methyl group in the tertiary benzylic radical would increase its oxidative ability; meanwhile, the carbonyl group potentially coordinates to $(\mathbf{L}^*)Cu^{II}Ar$, which could facilitate their interaction. Therefore, the carbonyl-substituted tertiary carbon-centered radical might be a good candidate to survey the possibility of the asymmetric arylation of the tertiary carbon-centered radicals.¹¹

On the basis of this hypothesis, several alkenes bearing various carbonyl groups were chosen to generate tertiary carboncentered radicals via CF₃ radical addition, which were tested for the asymmetric coupling with (L1)Cu^{II}Ar (Ar = p-^tBuC₆H₄, from 2a). As shown in Table 1A, the reaction of ketone 1a or ester 1b didn't give the desired arylation products; pleasingly, the amides 1c and 1d yielded the corresponding arylated products 3c and 3d in 40% and 48% yields, respectively, indicating that the acylamidyl groups did have a remarkable effect on the coupling of the tertiary carbon-centered radical with (L1)Cu^{ll}Ar species. Notably, the reaction of 1c gave the product 3c without enantioselectivity, while the enantioselective control was observed in the reaction of 1d, *albeit* giving the product 3d with 23% ee. Encouraged by these results, a series of bisoxazoline (Box) ligands were then examined for the reaction of 1d (see Table 1B and SI). Interestingly, the gem-disubstituted ligands have a significant effect on the reactivity and enantioselectivity. For instance, the ligand L2 bearing a gem-cyclopropyl group gave the product 3d in 35% yield with 8% ee; while the ligand L3 with gem-dibenzyl groups yielded the product 3d with better enantioselectivity (45% ee). Further variation of substituents in the oxazoline moiety revealed that the ligand L4 with benzyl groups remarkably increased the enantioselectivity of the product 3d (68% yield and 76% ee). Notably, the gem-dibenzyl groups are very crucial to the enantioselective induction of the radical coupling, switching the benzylic groups to an alkyl group diminished the *ee* value (e.g., L5 and L6), which might be attributed to a side-arm effect.¹² Interestingly, when the reaction in

Table 1. Optimization of the reaction conditions^{a,b}

CF₂

'n



methanol at 0 °C was conducted, both the yield and enantioselectivity were increased (up to 85% yield and 90% *ee*). Further copper catalyst screening showed that $Cu(OTf)_2$ could efficiently catalyze the reaction to afford the product **3d** in 93% yield with 90% *ee*.

After having established the optimal reaction conditions, the scope of this asymmetric arylation of the tertiary carbon-centered radicals was then investigated. As highlighted in Table 2A, electron-rich aryl boronic acids could be employed as coupling partners to yield the corresponding products 4-11 with excellent enantioselectivities (88-95% ee). Notably, compared to p- $CH_3C_6H_4B(OH)_2$ (4), the reaction of the *o*- $CH_3C_6H_4B(OH)_2$ gave the product 5 in a lower yield (80% vs 42%) but with a slightly higher enantioselectivity (90% vs 94% ee), because of a steric effect. In addition, aryl boronic acids bearing various halides also worked nicely to deliver the desired products 12-14 in good yields with excellent enantioselectivities (76-89% yield and 93-97% ee). Furthermore, aryl boronic acids bearing strong electronwithdrawing groups on the aromatic ring, which exhibited poor reactivities in our previous studies,^{7d-e} also performed very well to give the desired products 15-23 in good yields (53-87%) with excellent enantioselectivities (90-96% ee). Importantly, heteroaryl boronic acids, such as benzothiophene, pyridine and pyrimidine, were also suitable for the reaction to deliver the arvlation products 24-26 with excellent enantioselectivities (88-96% ee). It is noteworthy that a wide array of functional groups, such as halide, ether, thioether, CF₃, OCF₃, ketone, cyano, ester, nitro, acetal, and sulfonyl groups, could be well tolerated under our current reaction conditions. In addition, our reaction could be performed on a gram scale, yielding 1.28g of the desired product 12 in 67% yield without loss of enantioselectivity (93% ee). The absolute configuration of (S)-12 was unambiguously determined by X-ray crystallography.

Next, we examined the scope of the alkenes. As revealed in Table 2B, acrylamides with various aryl groups at the α -carbon position reacted smoothly with aryl boronic acids to provide the coupling products **27-32** bearing a quaternary all-carbon center with excellent enantioselectivities (89-98% *ee*). Moreover, aryl substituents at the nitrogen atom in acrylamides could also be variable to provide the corresponding products **33-36** in good yields with excellent enantioselectivities (87-94% *ee*). Notably, similar to the *N*-arylacryamides, the reaction of *N*-methyl acrylamide also proceeded smoothly to give product **37** in good result (75% yield, 86% ee).

As a challenging issue in our previous studies, the enantioselectively trapping of non-benzylic radicals by L*Cu(II)-FG species is not realized. Given that carbon-centered radicals can be stabilized by the adjoining acylamidyl groups, asymmetric trapping of the non-benzylic radicals by the L*Cu^{II}Ar species was further examined (Table 2C). Excitingly, the reaction of Nphenyl-a-methylacryamide with ortho-fluorophenyl boronic acid under the optimized conditions proceeded smoothly to afford the arylated product 38 in 71% yield with 92% ee; in addition, various aryl boronic acids bearing electron-withdrawing substituents, such as halides and carboxylic esters, proved to be good coupling partners to give the products 39-43 in satisfied vields with excellent enantioselectivities (86-93% ee). In comparison, the reaction of electron-rich aryl boronic acid, such as $p^{-t}BuC_6H_4B(OH)_2$, exhibited moderate reactivity to provide the desired product 44 in 49% yield, but with a slightly lower enantioselectivity (81% ee). Moreover, reactions of acrylamides bearing different alkyl groups at the α -position proceeded smoothly to yield the corresponding products 45-49 in moderate to good yields with excellent enantioselectivities (83-93% ee). Notably, acrylamides bearing the alcohol moiety were suitable for



Cu(CH₃CN)₄PF₆/L³

 $\frac{\text{ArB}(\text{OH})_2 \text{2a}}{(\text{Ar} = p^{-t}\text{BuC}_6\text{H}_4)}$

DCM/DMA(v/v = 4/1)

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^a Reaction conditions: **1** (0.2 mmol), Ar²B(OH)₂ **2** (0.4 mmol), Togni-I (0.3 mmol), Cu(OTf)₂ (0.02 mmol, 10 mol %), **L4** (0.024 mmol, 12 mol %) in MeOH (2.0 ml) at 0 °C. ^b Isolated yield, and enantiomeric excess (ee) were determined by HPLC or SFC on a chiral stationary phase. ^c Cu(CH₃CN)₄PF₆ was used as catalyst. ^d **12** (1.28 g) was obtained in 4.0 mmol scale. ^e ent-**L4** was used as chiral ligand. ^f Reactions were conducted in 0.4 mmol scale. ^g Reactions were conducted in 0.1 mmol scale.

the reaction to give the desired product **47** with 93% *ee, albeit* in a modest yield (44%). It was worthy noting that, the reactions were limited to the terminal alkenes, and β -substituted internal alkene exhibited low efficiency. Moreover, when substrate without substituent or bearing a steric bulky alkyl group (e.g. ^{*i*}Pr) at the α -position, the reaction also exhibited poor or no reactivity to yield the desired products (**50** or **51**).

To showcase the utility of our method, further transformations of the arylation products were investigated (Scheme 2). Sequential activation of the amidyl group and LiAlH₄ reduction of **4** delivered the chiral β , β -diaryl alcohol **52** in 59% yield. In addition, the direct reduction of **12** by BH₃·Me₂S yielded the γ -CF₃- β , β -diaryl propylamine **53** in 80% yield. Moreover, nucleophilic aromatic amination of **14** furnished the optically pure CF₃-containing oxindole **54** in 59% yield. Finally, removing the *p*-methoxyphenyl group in amide **33** by CAN afforded the free amide **55** in 51% yield. Notably, no obvious erosion of enantiomeric excess was observed in these transformations.



Consistent conditions. (a) (1) refer, then propyrelino continuet, DMAP, THP, 60 °C. (2) LiAlH₄, THP, rt -55 °C. (b) BH₃·Me₂S, toluene, rt -110 °C. (c) LiH, DMF, 130 °C. (d) CAN, CH₃CN/H₂O, 60 °C.

To gain more insight into the plausible radical mechanism, a radical scavenger CBr₄ was subjected to the standard reaction of 1d; the arylation was completely inhibited, but the bromination product 56 was obtained in 80% yield (Scheme 3A), indicating the involvement of benzylic radicals. In addition, the reaction of ketone 1a or ester 1b didn't provide any arylation products (Scheme 3B). For the case 1a, although the benzylic radical int-I couldn't be trapped by (L4)Cu^{II}Ar, its mesomer int-II reacted with $(L4)Cu^{II}Ar$ smoothly to yield the coupling product 3a' in 87% yield via the reductive elimination of Cu(III) species int-III (Scheme 3B and 3C).^{13a-b} The benzylic radical generated from 1b couldn't react with (L4)Cu^{II}Ar either, but only the self-coupling product 3b' was detected (Scheme 3B). In comparison, the benzylic radicals adjacent to an amidyl group (e.g., generated from 1c or 1d) could be trapped by $(L4)Cu^{II}Ar$ to give the arylation products 3c or 3d,^{13b-d} and the reaction rate of 1d was faster than that of 1c (Scheme 3D, left). We reasoned that, owing to the preferred geometry of *cis*-1c and *trans*-1d,¹⁴ the resultant benzylic radical int-IV produced from cis-1c is more sterically bulky than int-V generated from trans-1d (Scheme 3D, right). On the other hand, the slow reaction of the benzylic radical int-IV with (L4)Cu^{II}Ar species could allow 5-*exo-trig* cyclization of int-IV to give a small amount of the side product 3c';¹⁵ while the 5exo-trig cyclization did not occur in the reaction of 1d, because of the trans configuration of int-V. The product 3d was generated with higher enantioselectivity than 3c (80% ee vs 50% ee), revealing that the CONH moiety played a key role in the enantioselective trapping step, but the detailed mechanism is still unclear at the moment.¹⁶

In summary, the first asymmetric Cu-catalyzed trifluoromethylarylation of α -substituted acrylamides has been developed, where an enantioselective coupling of tertiary carboncentered radicals with (L4)Cu^{II}Ar acts as a key step to construct a quaternary all-carbon stereocenter. Further exploration of the mechanistic details and new asymmetric radical transformations based on the acylamide-substituted tertiary carbon-centered radicals are in progress in our laboratory.

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Scheme 3. Mechanistic studies, and all the reactions in part B were conducted at room temperature with $Cu(OTf)_2/L4$ as catalyst.

Supporting Information

Synthetic procedures, characterization, mechanistic study data, and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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14. Tertiary amides bearing a phenyl group and an unhindered alkyl group on the amidyl nitrogen atom exist predominately in a cis-form, while secondary amides are in a trans-form. In addition, the activation energies for the *cis/trans* isomerization of amides are usually high. For details, see: (a) Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. Preference for cis-Amide Structure in N-Acyl-N-Methylanilines. J. Am. Chem. Soc. 1992, 114, 10649. (b) Saito, S.; Toriumi, Y.; Tomioka, N.; Itai, A. Theoretical Studies on cis-Amide Preference in N-Methylanilides. J. Org. Chem. 1995, 60, 4715. (c) Dugave, C.; Demange, L. Cis-Trans Isomerization of Organic Molecules and Biomolecules: Implications and Applications. Chem. Rev. 2003, 103, 2475. (d) Hou, Z.; Mao, Z.; Song, J.; Xu. H.-C. Electrochemical Synthesis of Polycyclic N-Heteroaromatics through Cascade Radical Cyclization of Diynes. ACS Catal. 2017, 7, 5810. (e) Wu, Z.; Xu. H.-C. Synthesis of C3-Fluorinated Oxindoles through Reagent-Free Cross-Dehydrogenative Coupling. Angew. Chem. Int. Ed. 2017, 56, 4734.

15. When Cu(CH₃CN)₄PF₆ was used as catalyst, the reaction of 1c provided the arylation product 3c in 13% yield (49% ee) and the radical cyclization product 3c' in 28% yield. For details, see the SI.

16. We assumed that the CONH moiety in acrylamides would facilitate the interaction of the tertiary carbon-centered radicals with (L4)Cu^{II}Ar and enhance the enantioselectivity, which might involve the bonding of an oxygen of carbonyl or a nitrogen atom of amides to copper, but the detailed mechanism is unknown.

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