Enantioselective Catalysis

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Enantioselective Copper-Catalyzed Quinoline Alkynylation

*Mukesh Pappoppula, Flavio S. P. Cardoso , B. Owen Garrett, and Aaron Aponick**

Abstract: *A highly enantioselective copper-catalyzed alkynylation of quinolinium salts is reported. The reaction employs StackPhos, a newly developed imidazole-based chiral biaryl P,N ligand, and copper bromide to effect a three-component reaction between a quinoline, a terminal alkyne, and ethyl chloroformate. Under the reaction conditions, the desired products are delivered in high yields with ee values of up to 98 %. The transformation tolerates a wide range of functional groups with respect to both the alkyne and the quinoline starting materials and the products are easily transformed into useful synthons. Efficient, enantioselective syntheses of the tetrahydroquinoline alkaloids (+)-galipinine, (+)-angustureine, and (−)-cuspareine are reported.*

The tetrahydroquinoline (THQ) motif is an important structural construct found in a myriad of natural products and biologically active molecules.[1] While many substitution patterns are known within this broad family of compounds, a particularly important core constituent is substitution at the 2-position.[2] Examples are highly varied with respect to both structure and biological activity. Select examples include martinellic acid (**1**), a nonpeptide bradykinin antagonist,[2] torcetrapib (**2**), a recent hypocholesterolemia drug candidate[3] the THQ **3**, an acetyl-coA carboxylase 2 inhibitor,[4] and angustereine, a natural product with activity against *Mycobacterium tuberculosis* (Figure 1),[5] among countless others.[6]

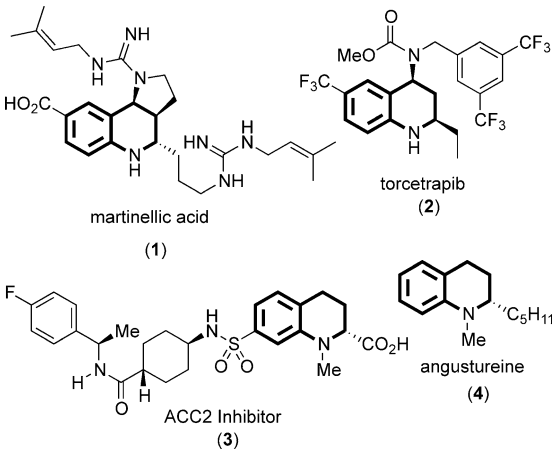

Figure 1. Select examples of biologically active tetrahydroquinolines.

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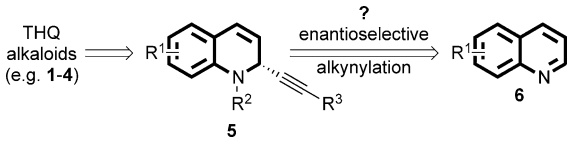
Owing to this importance, a variety of synthetic methods have been developed to access these molecules in both the racemic and scalemic sense. This work has been nicely reviewed in several comprehensive articles.[7] Generally speaking, some of the most broadly applicable methods of preparation include the Povarov reaction,[8] organocatalytic cascade reactions,[9] inverse electron demand aza-Diels–Alder reactions, and a variety of enantioselective reduction or hydrogenation reactions of substituted quinolines.[10] Considering these methods, it seems advantageous from a versatility standpoint, to stereoselectively introduce substitution at the quinoline C2-position, as the 2-substituted quinoline substrates required for reductive methods are often expensive or not commercially available. To this end, nucleophilic addition to aromatic heterocycles has been demonstrated as a highly versatile method.[11] These reactions can be conducted under a variety of conditions, including catalytic systems, and typically involve an N-alkylation/acylation event to generate an iminium ion, followed by addition of a nucleophile to afford the 1,2-adducts.[12]

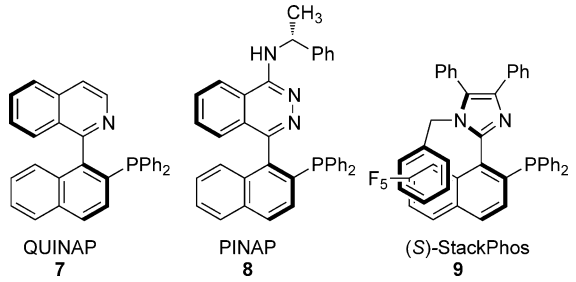
Examination of the tetrahydroquinolines shown in Figure 1 suggests that a unified approach to this class of molecules (e.g., **1**–**4**) might be developed from alkynes (**5**) by a straightforward functionalization of the carbon–carbon triple bond (Scheme 1). This approach could be realized



Scheme 1. Enantioselective alkynylation approach to THQ alkaloids.

using an enantioselective alkyne addition reaction to generate **5** from **6**. However, despite the significant attention from the synthetic community described above, an efficient catalytic enantioselective acetylide addition to quinolines has yet to be developed. Herein we report a highly enantioselective reaction that is tolerant of a wide variety of alkyne substitution and not dependent on the electronic nature of the quinoline starting material.

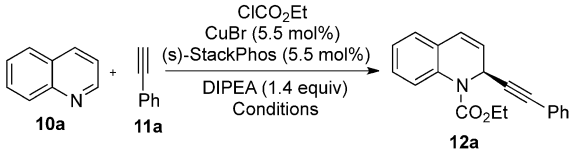
As part of a ligand development program exploring the use of StackPhos (**9**),[13] we became interested in the question of how to catalytically install alkynes at the quinoline C2 with stereocontrol, thus envisioning a new synthetic approach to martinellic acid (**1**).[2,14] P,N ligands such as QUINAP (**7**) and PINAP (**8**) have been reported for copper-catalyzed alkyne addition reactions. Interestingly, while Taylor and Schreiber reported the use of **7** in the enantioselective addition to isolated dihydroisoquinolinium salts,[15] satisfactory results were not obtained in the related reaction of the fully aromatic



quinolines.[16] After ligand screening, Arndtsen and co-workers found **8** to be the best ligand, but the highest selectivity reported was 84% *ee*.[16] Axially chiral P,N ligands appear to be optimal for this application but limited by the current state-of-the-art. A series of excellent ligands have been reported by the groups of Brown, Guiry, and Carreira among others.[17] These ligands share a common structural motif, more specifically, the biaryl system always consists of two six-membered aromatics that provide similar binding modes, which may be suboptimal in certain reactions.[17e] Encouraged by our success with StackPhos,[13] an axially chiral imidazole-based P,N ligand, we decided to investigate quinoline addition reactions as the electron-rich five-membered biaryl ring system with different dihedral and bite angles may help overcome this limitation.

To this end, we set out to screen reaction conditions employing (S)-StackPhos as a ligand in a copper-catalyzed three component coupling of quinoline, phenyl acetylene, and ethyl chloroformate (Table 1). Initial reaction conditions with a racemic ligand employed toluene as the solvent and, although somewhat slow, did cleanly afford the desired product **12a** in 50% yield (entry 1). While switching to acetonitrile had minimal effect (entry 2), the use of methylene chloride drastically improved the yield and reaction rate, thus providing **12a** in 92% yield in just 4 hours at room temperature (entry 3). These enhancements can likely be attributed to the solubility of the in situ generated quinolinium salt, which appeared to be readily soluble with dichloromethane. With excellent reactivity uncovered, we turned our attention to selectivity. Much to our delight, when the nonracemic **9** was employed under otherwise identical reaction conditions, **12a** was obtained in 93% *ee* (entry 4). Lowering the temperature increased the enantioselectivity to 95% *ee* and 98% *ee* at 0°C and −20°C, respectively, with a longer reaction time providing slightly diminished yields (entries 5 and 6). While the reaction conditions in entry 5 (0°C to room temperature) strike a good balance of yield and selectivity, using lower temperatures (−20°C) do indeed provide increased selectivity and the conditions in entry 6 were selected as standard conditions for the reaction.

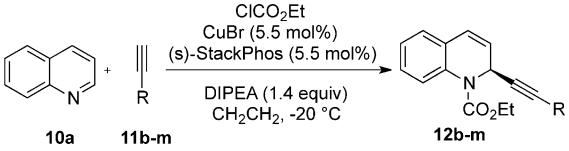
Table 1: Optimization studies.

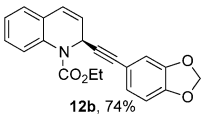
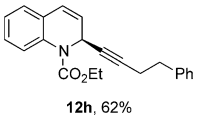
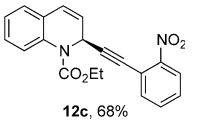
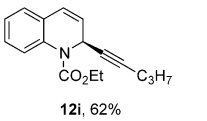
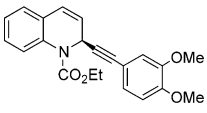
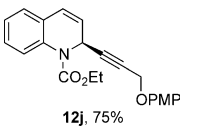
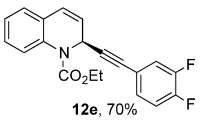
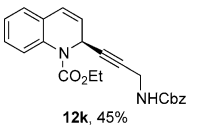
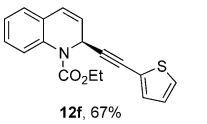
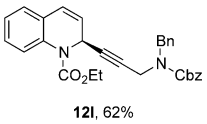
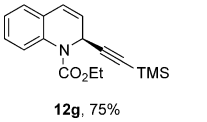
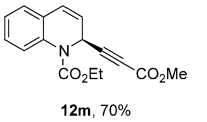


Entry[a]	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	toluene	RT	18	50	n.a.[d]
2	acetonitrile	RT	18	55	n.a.[d]
3	CH_2Cl_2	RT	4	92	n.a.[d]
4	CH_2Cl_2	RT	4	90	93
5	CH_2Cl_2	0 to RT	18	80	95
6	CH_2Cl_2	-20	22	74	98

[a] Reactions run with 1.0 equivalents of **10a**, **11a**, and ethyl chloroformate. [b] Yield of isolated product. [c] Determined by HPLC employing a chiral stationary phase. [d] Racemic StackPhos ligand employed. DIPEA = diisopropylethylamine.

Table 2: Substrate scope with respect to alkyne.



Entry	Product[a]	*ee* [%][b]	Entry	Product[a]	*ee* [%][b]
1	 **12b**, 74%	98	7	 **12h**, 62%	95
2[c]	 **12c**, 68%	96	8	 **12i**, 62%	92
3[c]	 **12d**, 86%	96	9	 **12j**, 75%	91
4[c]	 **12e**, 70%	96	10	 **12k**, 45%	90
5	 **12f**, 67%	90	11	 **12l**, 62%	90
6[c]	 **12g**, 75%	96	12	 **12m**, 70%	92

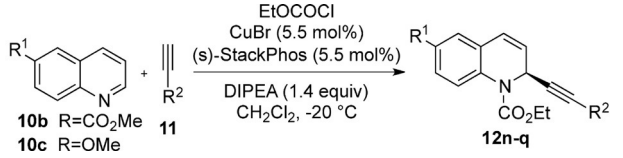
[a] Yield is that of the isolated product. [b] Determined by HPLC employing a chiral stationary phase. [c] Reaction temperature = 0°C to RT. Cbz = benzyloxycarbonyl, PMP = *p*-methoxyphenyl.

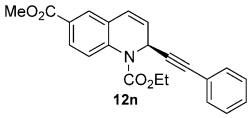
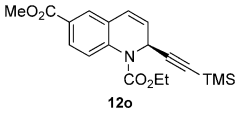
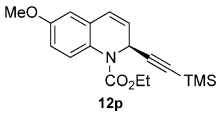
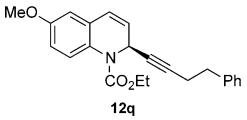
After establishing optimal reaction conditions, we explored the reaction scope with respect to the alkyne nucleophile (Table 2). It seemed particularly important to survey a variety of alkynes classes (aryl, alkyl, silyl, propiolate, heteroatom substituted, etc.) as all types of substrates would be required for THQ alkaloid syntheses. With this goal

in mind, the study commenced with aryl alkynes (**11b–f**) ranging from electron-rich to electron-deficient and heteroaromatics. As can be seen (entries 1–5), a variety of aromatic groups are well tolerated and provide the alkynylation products **12b–f** with extremely high *ee* values. Silyl-substituted alkynes such as trimethylsilylacetylene worked exceedingly well, thus yielding **12g** in 96% *ee* (entry 6) and even alkyl-substituted substrates perform quite well in the reaction (entries 7 and 8). Additionally, protected propargyl alcohols (entry 9) and propargyl amines (entries 10 and 11), as well as propiolates (entry 12) all smoothly afford the desired products in high enantiomeric excess.

It was also important to understand how the electronic character of the quinoline affects the reaction and this was briefly explored. Electron-donating and electron-withdrawing groups were included on **10b** and **10c**, respectively, and reactions with **11** were conducted under the standard reaction conditions (Table 3). As can be seen in each entry, very high

Table 3: Substrate scope with respect to quinoline.

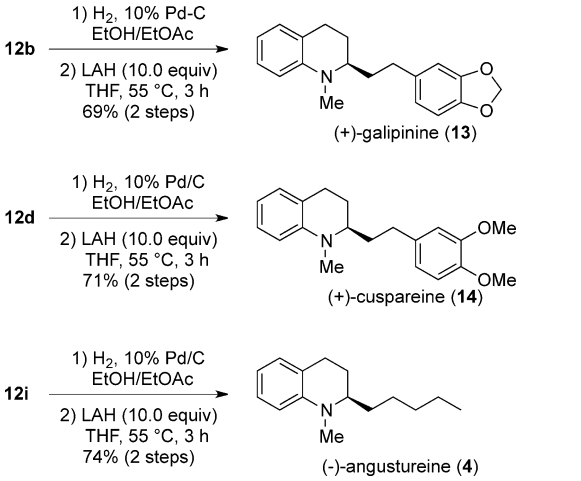


Entry	Product	Yield [%][a]	*ee* [%][b]
1	 12n	66	96
2	 12o	66	97
3[c]	 12p	80	90
4	 12q	77	92

[a] Yield of isolated product. [b] Determined by HPLC employing a chiral stationary phase. [c] Reaction temperature = 0 °C to RT. TMS = trimethylsilyl.

ee values were achieved. While electron-deficient quinolines afforded slightly lower chemical yields, electron-rich quinolines smoothly provided the products, thus further expanding the reaction scope.

This broad substrate scope is, to the best of our knowledge, unknown in catalytic enantioselective alkynylation reactions. It is particularly noteworthy that alkyl- and propargyl-substituted alkynes function well in the reaction. While compounds such as **12g** could be desilylated and further functionalized, this methodology should obviate the need for such manipulations and enable highly convergent synthetic strategies to tetrahydroquinolines.[14] However, for synthetic applications the absolute configuration of the products needs to be determined. To do so, we applied our methodology to the synthesis of three tetrahydroquinoline alkaloids, (+)-galipinine (**13**),[18] (+)-cuspareine (**14**),[19] and (−)-angustureine (**4**),[5] which are natural products isolated from the bark of *Galipea officinalis* Hancock, and have well-documented absolute configuration and optical rotation data. With (*S*)-StackPhos (stereochemistry depicted as in **9**), **12b**, **12d**, and **12i** were produced in high *ee* value with heretofore unknown absolute stereochemistry (Table 2). For conversion into the natural products, reduction of the olefin and alkyne moieties and transformation of the ethyl carbamate into an N-methyl group was required. This conversion was readily accomplished in two steps by hydrogenation and reduction of the carbamate (Scheme 2). In each case, the sign and magnitude of the rotation nicely corresponded to previously reported values[20] and allowed the stereochemical assignment shown in Scheme 2.



Scheme 2. Assignment of absolute configuration by alkaloid synthesis.

The likely mechanistic scenario for this reaction involves generation of a quinolinium salt followed by acetylide addition with the chiral (S)-StackPhos complex **15** (Figure 2). A possible rationale for the absolute stereochemistry observed using the C_1-symmetric complex **15** must rely on the chiral biaryl axis creating a chiral environment around the metal center. With biaryl ligands such as BINAP, this is achieved by arrangement of the phenyl groups in a propeller-shaped orientation, thus efficiently transmitting the chiral information towards the reactive center.[21] In StackPhos complexes, this likely occurs in a similar fashion with the phenyl groups on the phosphine and the proximal phenyl group on the imidazole, as seen in **16** (blue phenyl groups), represented as the quadrant diagram **17**. To preserve the Burgi–Dunitz angle, the addition must occur either via the quinolinium ion **18** or **19**. Considering both the steric environment and the stereochemistry of the observed products, the addition likely occurs via **19** to minimize steric interactions and produce the alkyne **20**.

In conclusion, we have developed a new catalytic enantioselective method for the dearomative alkynylation of

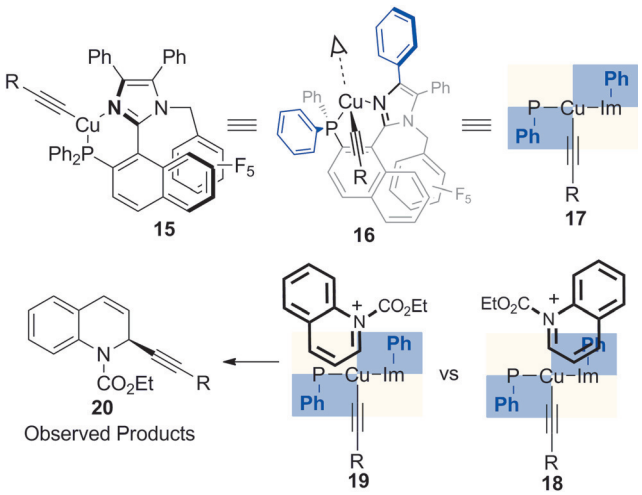


Figure 2. Working stereochemical model. Im = imidazolyl.

quinolines enabled by use of the ligand StackPhos. The reaction is high yielding, operationally simple, and delivers the products in high enantiomeric excess under mild reaction conditions. The absolute configuration of the products was assigned by conversion into *galipea* alkaloids with known optical rotation, and an extremely broad range of substrates with regard to both the alkyne and quinoline was demonstrated. This should allow application of the method in complex molecule synthesis, which is underway in our laboratory and will be reported in due course.

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Keywords: alkynes · copper · heterocycles · ligand design · synthetic methods

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