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Highly enantioselective catalytic addition of Grignard reagents to *N*-heterocyclic acceptors

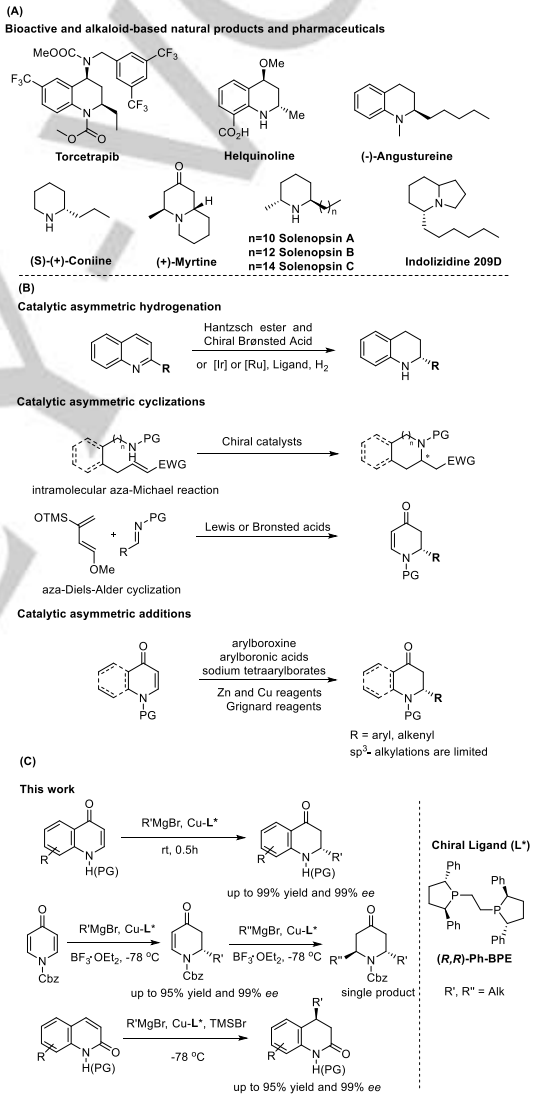
Yafei Guo, and Syuzanna R. Harutyunyan*

Abstract: General methods to prepare chiral *N*-heterocyclic molecular scaffolds are greatly sought after due to their significance in medicinal chemistry. Here we describe the first general catalytic methodology to access a wide variety of chiral 2- and 4-substituted tetrahydro-quinolones, dihydro-4-pyridones and piperidones with excellent yields and enantioselectivities, utilizing a single catalyst system.

Optically active piperidine and tetrahydroquinoline derivatives are ubiquitous structural motifs in alkaloid-based natural products, and bioactive and pharmaceutical compounds. Some examples to be highlighted include *Torcetrapib,* a drug used to treat elevated cholesterol levels, the antibiotic *Helquinoline,* as well as various alkaloids such as the *Angustureine, Coniine, Myrtine, Solenopsin* series and *Indolizidine* (Scheme 1, A).[1] Accordingly, chiral piperidine and tetrahydroquinoline derivatives represent important synthetic targets. General asymmetric synthetic routes for their synthesis rely on several strategic approaches (Scheme 1, B). Some of the most developed routes to chiral substituted tetrahydroquinolines make use of catalytic asymmetric hydrogenation of quinoline derivatives using chiral transition metal complexes and transfer hydrogenations by chiral Brønsted acids with Hantzsch esters.[2] Efficient catalytic asymmetric synthesis to access chiral hydroquinoline, quinolone and piperidone derivatives using intramolecular aza-Michael and aza-Diels-Alder reactions catalyzed by Lewis or Bronsted acids have been also explored.[3]

Other potential alternative *N*-heterocyclic precursors for the synthesis of chiral piperidine and tetrahydroquinoline derivatives include piperidones, dihydropyridones and quinolones, which in addition are often found as part of more complex biologically active compounds.[4] A common strategy that can access these precursors is the asymmetric conjugate addition of organometallics to *N*-heterocyclic acceptors using chiral auxiliaries.[5] However, *catalytic* enantioselective methodologies for conjugate additions to for example quinolone, pyridone, dihydropyridone and to acylpyridinium salts would constitute more attractive routes. Several such methods for additions of organometallics to 4-quinolones and dihydropyridone have been developed to date, with the most successful examples focusing on arylations.[6] In contrast, for asymmetric alkylations there are only few reports, which make use of dihydropyridone[6f,g] and acylpyridinium salt.[7,1a,8b] These alkylation methods suffer from limited product scope with either low yields or moderate enantioselectivities. Furthermore, catalytic asymmetric alkylation of 4-quinolones and catalytic asymmetric conjugate additions in general to 2-quinolones as well as 4-pyridone[8] are unknown. In pursuit of a catalytic asymmetric approach to a wide variety of chiral *N*-heterocyclic compounds we were interested in developing a single catalytic system capable of harnessing the reactivity of various *N*-heterocyclic acceptors.

Herein, we describe the first general protocol for catalytic asymmetric addition of various Grignard reagents to a wide variety of *N*-heterocyclic acceptors with excellent yields and enantioselectivities (Scheme 1, C), requiring a single catalytic system based on copper salt and chiral diphosphine ligand.



Scheme 1. (A) Examples of pharmaceuticals and natural products featuring chiral *N*-heterocyclic core (B) State of the Art (C) This work.

Our initial studies focused on the development of an efficient catalytic methodology for the alkylation of 4-quinolones (Table 1). To compensate for the relatively low reactivity of the 4-quinolone acceptor, we decided to take advantage of the high reactivity of Grignard reagents. For the screening of catalytic systems and reaction conditions we chose the addition of EtMgBr to

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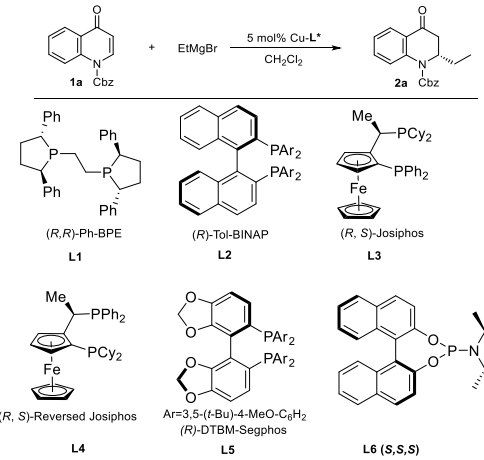
carboxybenzyl-protected (Cbz) 4-quinolone **1a** as model reaction. Addition of EtMgBr in the absence of any catalyst did not provide substrate conversion, even at room temperature (entry 1).

Table 1. Optimization of reaction conditions for the addition of EtMgBr to *N*-Cbz-4-quinolone **1a**.[a]



Entry	T (°C)	Time (h)	Ligand	Yield (%)[b]	*ee* (%)[c]
1[d]	Rt	2	-	0	0
2	-78	12	**L1**	99	99
3	-20	2	**L1**	99	99
4	0	2	**L1**	99	98
5	Rt	0.5	**L1**	98	98
6	Rt	0.5	**L2**	21	28
7	Rt	0.5	**L3**	78	27
8	Rt	0.5	**L4**	82	57
9	Rt	0.5	**L5**	32	0
10	Rt	0.5	**L6**	71	0

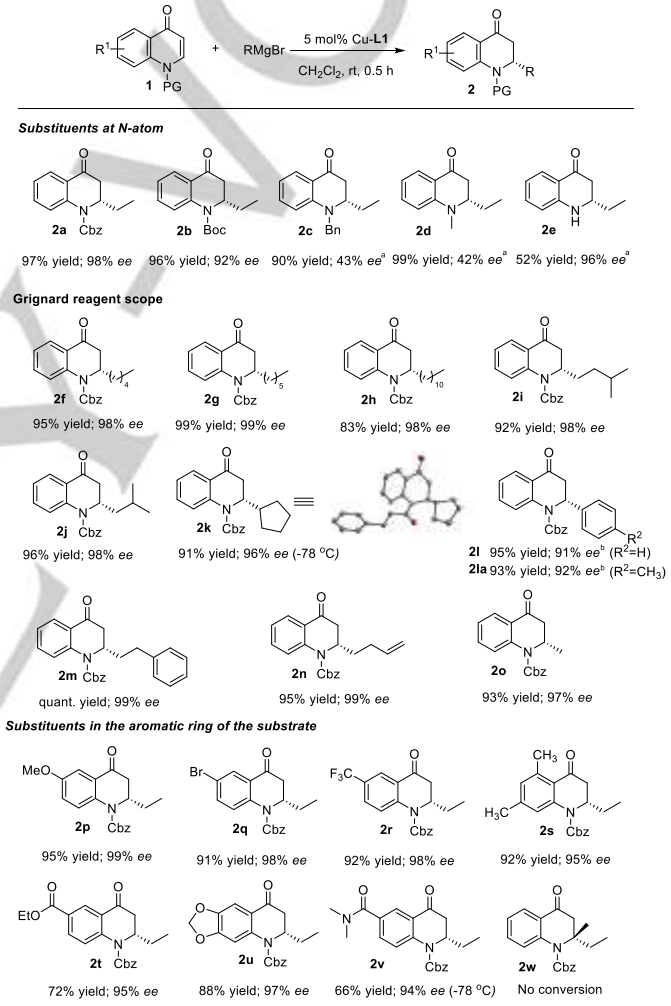
[a]Reaction conditions: *N*-Cbz-4-quinolone **1a** (0.2 mmol), EtMgBr (2.0 equiv.), Ligand **L** (6 mol%), CuBr·SMe_2 (5 mol%) in CH_2Cl_2 (2 mL). [b]Yields are those for the isolated products. [c]The enantiomeric excess was determined by HPLC on a chiral stationary phase. [d]Reaction without CuBr·SMe_2 and ligand.

First we set out to identify promising chiral catalysts, using 5 mol% of CuBr·SMe_2 and 6 mol% of various chiral diphoshine (**L1-L5**) and phosphoarmidite (**L6**) ligand (Table 1). To our delight, using chiral diphosphine ligand **L1,** developed by Pilkington et al.,[9] the reaction proceeded to completion in 12 h at -78 °C providing the isolated final product **2a** in 99% yield and with 99% of enantiomeric excess. Optimization of the reaction temperature (entries 2-5) allowed us to establish highly practical conditions in which the addition product can be obtained at room temperature in only 20-30 min with a yield and enantiomeric purity of 98% (entry 5). This result is remarkable in its own right, as it represents the first example of highly enantioselective catalytic conjugate addition of Grignard reagents at room temperature.[10]

Further ligand screening revealed that none of the other diphosphine-type ligands **L2-L5**, nor phosphoramidite-type ligand **L6**, work for this chemistry both in terms of yield and enantioselectivity (entries 6-10). This is rather surprising, as all of these ligands are normally very efficient in Grignard additions to more conventional Michael acceptors.[11]

Based on these results we adopted the following optimized conditions for further substrate scope studies: CuBr·SMe_2 (5 mol%), (*R,R*)-**L1** (6 mol%), Grignard reagent (2.0 equiv,), in CH_2Cl_2 for 30 min at room temperature.

Next, we evaluated EtMgBr with quinolones featuring various substituents at the *N*-atom (Scheme 2). We found that quinolones with electron withdrawing groups such as Cbz and Boc are well tolerated and give the corresponding products (**2a** and **2b**) with excellent yields and enantiomeric excess. However, for less reactive *Bn*- and *Me*-protected quinolones the addition products **2c** and **2d** can only be isolated in the presence of Lewis acid (TMSBr) with good yields and moderate 42-43% *ee*. Importantly, the addition of EtMgBr to unprotected quinolone substrate in the presence of TMSBr provided the corresponding product **2e** with 52% yield and 96% *ee*).



Scheme 2. Scope of the reaction between *N*-Cbz-4-quinolone substrates **1** and organomagnesium reagents. Reaction conditions: *N*-Cbz-4-quinolones **1** (0.2 mmol), EtMgBr (2.0 equiv.), ligand **L1** (6 mol%), CuBr·SMe_2 (5 mol%) and CH_2Cl_2 (2 mL) at room temperature for 0.5 h. [a] Reactions with quinolones **1c-1e** were carried out in the presence of TMSBr (2.0 equiv.) at -78 °C for 12 h. Absolute configuration of **2k** was established by X-ray crystallography. [b]PhMgBr and *p*TolMgBr were added slowly via a syringe pump in 2 h at 0 °C.

Having established the effect of the substituents at the nitrogen atom of the quinolone we explored the scope of Grignard reagents with *N*-Cbz-4-quinolone **1a**. We were pleased to find

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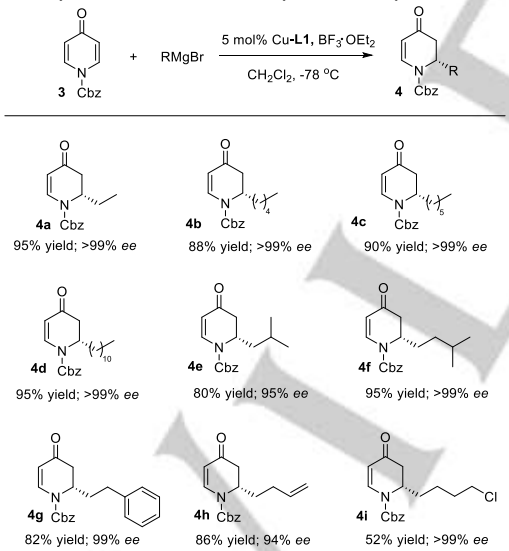
that our catalytic system enables the addition of a wide variety of alkyl Grignard reagents, including linear, *α*-, *β*- and *γ*-substituted, functionalized PhMgBr and *p*TolMgBr, providing products **2f-2n** all with excellent results. This even extended to the markedly less reactive MeMgBr, for which product **2o** was obtained with 93% yield and 97% enantiomeric excess.

Subsequently we examined the scope of the *N*-Cbz-4-quinolone substrates and found that substrates bearing functional groups such as *Me, Br, CF_3*, ether, amide or ester at the 5, 6, and 7-position, were all converted to the corresponding final products (**2p-2v**) successfully. In all cases, our optimized system afforded the products in excellent yields (66% to 99%) and enantioselectivities (*ee*s 94% to 99%). However, when 2-*Me*-*N*-Cbz-4-quinolone was used as a substrate, a lack of reactivity prevented the formation of addition product **2w** with quaternary stereocenter.

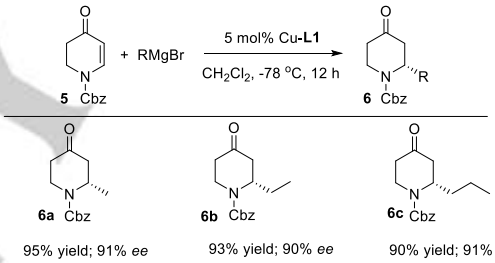
To expand this strategy towards the synthesis of chiral dihydro-pyridones and piperidones, we hypothesised that this protocol could also enable addition reactions to *N*-Cbz-4-pyridone **3** (Scheme 3). This substrate is more challenging for applications in catalysis as its aromatic character reduces the reactivity towards nucleophilic additions. As a result, pyridones have been hardly explored in asymmetric catalysis,[8] even though there is major potential in the application of these substrates in chemical synthesis: after the initial conjugate addition reaction the resulting chiral *N*-heterocyclic product with remaining Michael acceptor functionality can subsequently undergo further stereoselective functionalisations to provide 2,6-substituted chiral pyridines that can be very useful for natural product synthesis. We initially evaluated the reactivity of substrate **3** towards nucleophilic addition of EtMgBr using the reaction conditions optimized for *N*-Cbz-4-quinolones (Table 1, entry 2).



Scheme 3. Scope of the reaction of *N*-Cbz-4-pyridone **3** with organomagnesium reagents. Reaction conditions: *N*-Cbz-4-pyridone **3** (0.2 mmol), Grignard reagents (2.0 equiv.), Ligand **L1** (6 mol%), $BF_3{\cdot}OEt_2$ (2.0 equiv.), $CuBr{\cdot}SMe_2$ (5 mol%) and CH_2Cl_2 (2 mL) at -78 °C for 12 h.

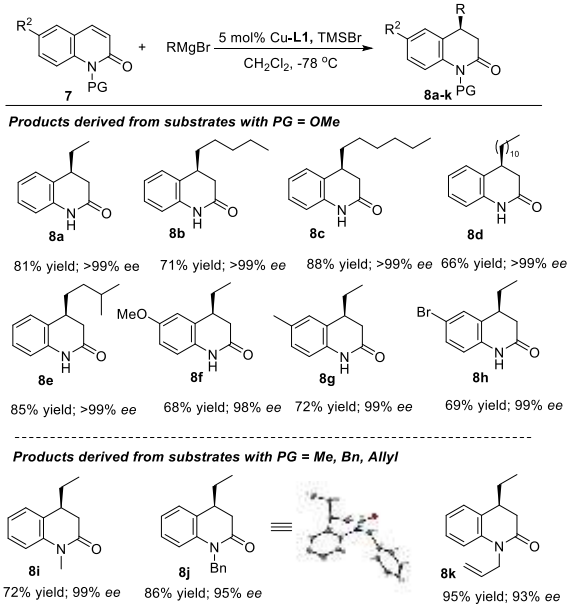
Unfortunately the corresponding addition product **4a** was not obtained, but instead the side products derived from the addition of EtMgBr to the carboxybenzyl moiety were found.[12] In order to steer the chemoselectivity of the reaction towards conjugate addition product **4a**, we decided to introduce Lewis acids.[8a,b] With $BF_3{\cdot}OEt_2$ as Lewis acid the best possible results, with 95% yield and more than 99% enantiomeric purity, were obtained (Scheme 3).[13] With this reaction conditions we assessed the scope of organomagnesium reagents for this reaction system (Scheme 3). A number of chiral 2-substituted 2,3-dihydro-4-pyridone products derived from the addition of linear (**4a-4d**), *β*-, and *γ*-branched (**4e-4f**) and functionalized (**4g-4i**) Grignard reagents were synthesized with high yields. In all cases excellent enantioselectivities were observed as well (*ee*s 94% to >99%).

Although asymmetric conjugate addition of arylboronic acid, aryl and dialkylzinc nucleophiles to *N*-substituted-2,3-dihydro-4-pyridones has been well explored in recent years[5,6f,g] we were interested to investigate the behavior of our catalytic system when applied to these substrates. Given their substantially higher reactivity than *N*-Cbz-4-pyridone we anticipated that Lewis acids are not needed and that low temperatures will most likely be required to avoid non catalyzed addition of Grignard reagents. Indeed, quick screening of several Grignard reagents, namely MeMgBr, EtMgBr and *n*PrMgBr supported this notion and the corresponding chiral 2-substituted 4-piperidones (**6a-6c**) were obtained with excellent yields and enantiomeric excesses above 90% (Scheme 4).



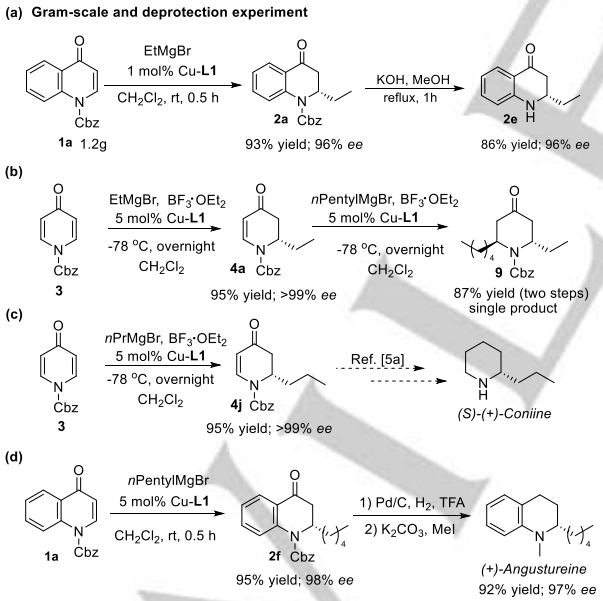
Scheme 4. Scope of the reaction of *N*-Cbz-2,3-dihydro-4-pyridone **5** with organomagnesium reagents. Reaction conditions: *N*-Cbz-2,3-dihydro-4-pyridone **5** (0.2 mmol), EtMgBr (2.0 equiv.), Ligand **L1** (6 mol%), $CuBr{\cdot}SMe_2$ (5 mol%) and CH_2Cl_2 (2 mL), -78 °C for 12 h.

Our next quest was to access chiral products derived from additions to *N*-substituted-2-quinolones that are formally cyclic α,β-conjugated amides and expected to be less reactive than 4-quinolones (Scheme 5). We were pleased to find that when using 2-quinolones with an OMe protecting group at the *N*-atom the corresponding deprotected products **8a-8h** were obtained with excellent enantiomeric excess and chemical yields. However, to reach full conversion and high yields it is necessary to use a Lewis acid, with TMSBr performing best. Importantly, the methoxy substituent at the *N*-atom is removed upon reaction work up. Using this reaction protocol we obtained a variety of products using various Grignard reagents as well as substrates with different substituents in the aromatic ring. It is noteworthy that this catalytic system tolerates 2-quinolone substrates with various protecting groups at the *N*-atom such as *Me*, *Bn* and *Allyl*. The products **8i-8k**, derived from conjugate addition of EtMgBr to these substrates, were obtained with enantiomeric purities above 93% and yields above 72%.



Scheme 5. Scope of conjugate addition reactions of organomagnesium reagents to *N*-protected 2-quinolones **7**. Reaction conditions: 2-quinolone **7** (0.2 mmol), EtMgBr (2.0 equiv.), Ligand **L1** (6 mol%), TMSBr (2.0 equiv.), $CuBr{\cdot}SMe_2$ (5 mol%) and CH_2Cl_2 (2 mL), -78 °C for 12 h. Absolute configuration of **8j** was established by X-ray crystallography.

Finally, to demonstrate the potential applications of our reaction protocol, we carried out a gram-scale reaction as well as several additional transformations, all depicted in Scheme 6.



Scheme 6. Gram-scale reaction and useful derivatisations.

In summary, we have developed the first general protocol for the alkylation of various classes of *N*-heterocyclic electrophiles with organomagnesium, utilizing one catalytic system based on Cu(I) complex with (*R*,*R*)-Ph-BPE. Alkylation of 2-quinolones, 4-quinolones and 4-pyridones provides easy access to various derivatives of chiral 2- and 4-substituted tetrahydroquinolones and dihydro-4-pyridones in excellent yields and enantioselectivities. Significantly, addition reactions to *N*-substituted-4-quinolones can be carried out at room temperature, while consecutive alkylation of pyridone and the resulting 2,3-dihydro-4-pyridones allows for a convenient catalytic access to 2,6-substituted diastereomerically and enantiomerically pure piperidones. We anticipate that this methodology will be a valuable synthetic tool and find practical application in the synthesis of complex building blocks and natural and pharmaceutical compounds.

Acknowledgements

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Keywords: asymmetric catalysis • Grignard reagent • copper • alkaloid synthesis• alkylation

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[12] For the optimization data see SI.

[13] In contrast with 4-quinolone, this reaction does not work at room temperature due to compatibility issues between $BF_3{\cdot}OEt_2$ and the Grignard reagent at this temperature. For effect of Lewis acids in asymmetric catalysis and their compatibility with Grignard reagents see: a) J. Rong, R. Oost, A. Desmarchelier, A. J. Minnaard, S. R. Harutyunyan. *Angew. Chem. Int. Ed*. **2015;** *54*, 3038-3042; b) R. P. Jumde, F. Lanza, M. J. Veenstra, S. R. Harutyunyan. *Science* **2016**, *352*, 433-437; c) M. Rodríguez-Fernández, X. Yan, J. F. Collados, P. B. White, S. R. Harutyunyan, *J. Am. Chem. Soc.* **2017**, *139*, 14224-14231; d) R. P. Jumde, F. Lanza, T. Pellegrini, S. R. Harutyunyan. *Nat. Commun*. **2017**, *8*, 2058.

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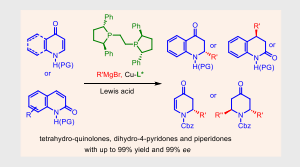
General catalytic protocol to access various derivatives of chiral 2- and 4-substituted tetrahydroquinolones, dihydro-4-pyridones and 2,6-substituted piperidones has been developed.



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Layout 2:

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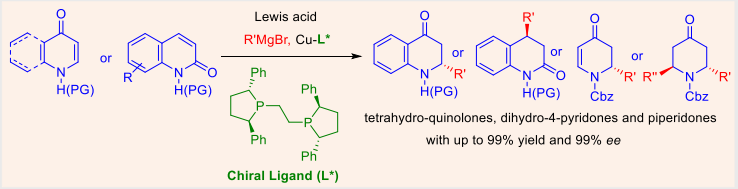

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