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Asymmetric Catalysis

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Copper-Catalyzed Enantioselective Alkylation of Enolizable Ketimines with Organomagnesium Reagents

Pablo Ortiz, Juan F. Collados, Ravindra P. Jumde, Edwin Otten, and Syuzanna R. Harutyunyan*

Abstract: Inexpensive and readily available organomagnesium reagents were used for the catalytic enantioselective alkylation of enolizable *N*-sulfonyl ketimines. The low reactivity and competing enolization of the ketimines was overcome by the use of a copper–phosphine chiral catalyst, which also rendered the transformation highly chemoselective and enantioselective for a broad range of ketimine substrates.

The asymmetric addition of organometallic reagents to C=N double bonds is a fundamentally important transformation that provides direct access to enantiomerically enriched α -chiral amines, which are important building blocks in organic synthesis and abundantly present motifs in biologically active compounds.^[1] Hence, numerous variants of this reaction, with different imine derivatives and organometallic reagents, have been tested with the aim of achieving high levels of reactivity and selectivity.^[2]

Among the different approaches for the synthesis of highly valuable enantiomerically enriched amines, a chiral-auxiliary strategy involving the use of Ellman *tert*-butylsulfonimines in combination with an organometallic reagent is often the method of choice.^[3] On the other hand, catalytic asymmetric methods are highly attractive, since only a small quantity of a precious chiral ligand is needed. In this context, the first catalytic asymmetric addition of nonstabilized organometallic reagents to aldimines through Lewis base activation by Soai et al. and, a few years later, the Lewis acid activated copper-catalyzed addition of organozinc reagents to aldimines by Tomioka and co-workers were important steps.^[4a,b] These initial reports triggered intensive research effort in this area, and a number of successful catalytic asymmetric methods for addition to aldimines were developed as a result.^[4c–f,2a,b,d,f] In contrast, progress in the catalytic asymmetric addition of organometallic reagents to ketimines to give amines with a tertiary stereogenic center at the α position has been much slower and remains a challenge owing to the poorer electrophilicity of ketimines and the more difficult enantiodiscrimination between the two substituents on the prochiral azomethine carbon atom.^[2b,c,e] Although several elegant examples of the arylation, alkynylation, and allylation of ketimines have been reported recently,^[5] the reactivity and

selectivity issues described above are particularly challenging for alkylation, which even now is restricted to the methylation and ethylation of a small set of activated ketimines.^[6]

Since the lower electrophilicity of ketimines is one of the major problems for this type of chemistry, the use of strong nucleophiles could be advantageous. Highly reactive organomagnesium (Grignard) reagents, which are the most commonly used organometallic reagents both in the laboratory and in industry,^[7] would be ideal for tackling the low reactivity of the ketimines. However, so far Grignard reagents have only been used in combination with chiral ketimines derived from the Ellman auxiliary.^[3] It is not surprising that they have not been used more widely for such transformations, as the uncatalyzed addition of the Grignard reagent is a formidable competitor. Furthermore, higher nucleophilicity goes hand in hand with increased basicity, which can cause deprotonation and thus enamide formation when enolizable ketimines are used.^[8] Consequently, catalytic asymmetric addition reactions of Grignard reagents to enolizable ketimines have remained elusive.

Over the past few years, our research group has pursued the synthesis of chiral molecules by the copper-catalyzed asymmetric alkylation of conjugated systems and carbonyl compounds.^[9] Herein we report the first catalytic asymmetric addition of alkyl Grignard reagents to enolizable ketimines. The corresponding alkylated products were obtained in high yield with high enantioselectivity.

To address the poor reactivity of the azomethine carbon atom, we focused on *N*-sulfonyl- and *N*-phosphinoyl-protected ketimines. A model reaction between ketimines **1** and hexylmagnesium bromide (HexMgBr) was used for the screening of suitable conditions for the catalytic asymmetric alkylation of acetophenone-derived imines (Table 1). The diphenylphosphinoyl-protected ketimine **1a** was tested in the presence of a catalytic system derived from CuBr·SMe₂ salt and the diphosphanylferrocene ligand **L1** at –60 °C.^[10] The chemoselectivity of the reaction was poor, and analysis of the crude reaction mixture by NMR spectroscopy revealed a complex mixture of products and ketimine **1a** (Table 1, entry 1). The starting material **1a** remained owing to either incomplete conversion or competing enolization. The crude reaction mixture also contained a reduction product, the result of yet another competing reaction through Meerwein–Ponndorf–Verley reduction of the ketimine.^[9c] We were able to increase the selectivity towards the addition product by using a Lewis acid mixture composed of BF₃·OEt₂ and CeCl₃^[9c] (entry 2). However, the enantioselectivity was low, and any further attempted optimization with this substrate was not successful. This result, together with the ease of hydrolysis of diphenylphosphinoyl imines, led us to explore

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Table 1: Optimization of the reaction conditions.

Entry ^[a]	Imine	L*	T [°C]	Solvent	1/2/3 [%] ^[b]	ee [%] ^[c]
1	1a	L1	−60	toluene	mixture	n.d.
2 ^[d]	1a	L1	−60	toluene	16:78:6	10
3 ^[d]	1b	L1	−78	toluene	41:59:0	30
4	1b	L2	−78	MTBE	26:74:0	24
5	1c	L2	−78	MTBE	20:70:10	12
6	1d	L2	−78	MTBE	73:27:0	30
7	1e	L2	−78	MTBE	11:89:0	33
8	1e	L1	−78	MTBE	58:42:0	59
9	1e	L1	−50	MTBE	29:71:0	62
10	1e	L1	−50	Et ₂ O	21:79:0	66
11	1e	L1	−50	Et ₂ O/MTBE	17:83:0	74

[a] Reaction conditions: [1] = 0.1 M, reaction time: 16–20 h, (0.1 mmol), [b] Conversion was estimated by ¹H NMR spectroscopy. [c] The ee value was determined by HPLC on a chiral stationary phase. [d] Additives (BF₃OEt₂/CeCl₃, 1 equiv of each) were used. Cy = cyclohexyl, MTBE = methyl *tert*-butyl ether.

sulfonamide protecting groups. Moderate conversion and encouraging enantiodiscrimination were observed in the addition of HexMgBr to the acetophenone-derived tosyl ketimine **1b** (entry 3). To our regret, extensive screening (see Table S1 in the Supporting Information) did not reveal superior ligands. Nevertheless, we found that ligand **L2** gave comparable results to **L1**, but, interestingly, with better chemoselectivity, since the formation of the reduction side product was diminished (Table 1, entry 4). Therefore, further optimization studies were carried out with ligand **L2**. To evaluate the effect of the steric nature of the protecting group, we tested different sulfonyl protecting groups. Use of the smaller ketimine **1c** with a methanesulfonyl (Ms) group, instead of ketimine **1b** with a toluenesulfonyl (Ts) group, provided the addition product **2c** with lower enantioselectivity (entry 5). On the other hand, ketimine **1d** with a 2,4,6-trimethylbenzenesulfonyl protecting group underwent the addition reaction with slightly higher enantioselectivity, but lower conversion.

Surprisingly, the use of ketimine **1e** with a bulkier *tert*-butylsulfonyl (Bus) group led to an increase in conversion towards the addition product to 89 % (Table 1, entry 7). At this stage, **L1** was evaluated again, and to our delight it showed very promising asymmetric induction of 59 % ee (entry 8). However, the conversion towards the addition

product was only 42 %. Importantly, increasing the reaction temperature had a positive effect, and at −50 °C, the conversion increased to 71 % (entry 9). The last reaction parameter studied was the solvent. It was found that diethyl ether was a more effective solvent for this system than MTBE, but that a mixture of both was the optimal reaction medium (Table 1, entries 10 and 11).

The optimized reaction conditions were applied to a wide range of aryl alkyl ketimines, and the procedure proved to be robust, giving excellent results in most cases (Scheme 1).^[11] We first analyzed the effect of the alkyl chain in the imine. Unexpectedly, the introduction of just one more carbon atom led to increased reactivity and full conversion to give the addition product **5a** in 90 % yield. Even more surprisingly, the ee value reached 90 %. This result was further improved with ketimine **4b**, which bears a propyl chain. The corresponding amine **5b** was isolated in quantitative yield and with excellent 97 % ee. This unusual enhancement of the reactivity with an

Scheme 1. Scope of the reaction with respect to the ketimine substrate. Reaction conditions: [1a], [4a-r] = 0.1 M, 16–20 h. Yields are for the isolated product; ee values were determined by HPLC on a chiral stationary phase. Absolute configurations were assigned by analogy with the literature (see the Supporting Information).

increase in the number of aliphatic carbon atoms in the molecule is similar to the improvement observed when changing from ketimine **1b** to **1e**. In each case, the effect can be attributed to the increased solubility of both the substrate and the corresponding reaction intermediates formed with the chiral Cu catalyst.^[12] Giving further credence to the trend in the reactivity, product **5c** with a butyl chain was obtained in quantitative yield with 91 % *ee*.

α -Branched imines could not be synthesized because the corresponding enamine was formed instead. Nevertheless, the β -branched imine **4d** could be prepared and proved to behave similarly to the ketimines with linear alkyl substituents. Finally, we determined the configuration of ketimine **4c** by 1D NOE experiments and obtained definitive proof by single-crystal X-ray diffraction (see the Supporting Information).^[13]

Next we studied the different substitution patterns of the aromatic ring of the ketimines. Both electron-rich and electron-deficient substituents were tolerated by this catalytic system (Scheme 1). The use of ketimine **4e** with a weakly electron donating methyl group in the *para* position did not pose a problem for the reaction, and the corresponding addition product **5e** was isolated in excellent yield (96 %) and enantioselectivity (95 % *ee*). Ketimine **4f** with a strongly electron donating methoxy group was tolerated as well, although somewhat lower enantioselectivity was observed (**5f**, 84 % *ee*). In the case of a bromine-substituted ketimine, the respective product **5g** was isolated in quantitative yield with 94 % *ee*. Similarly, the reaction conditions were also compatible with the strongly electron withdrawing CF₃ group (products **5h** and **5i**).

Steric effects were evaluated next. Not only *para*-substituted substrates, but also substrates with a *meta* substituent reacted smoothly: The *meta*-chloro-substituted product **5j** was obtained in excellent yield and enantioselectivity (Scheme 1). When a fluorine substituent was present in the *ortho* position, the corresponding product **5k** was obtained in 98 % yield with 96 % *ee*. A further increase in steric bulk by the replacement of the fluorine substituent in the *ortho* position with a methyl group made the corresponding ketimine unreactive. We were particularly interested in performing this reaction with functionalized ketimines to give products that would be amenable to further transformation after the addition of the Grignard reagent. These highly reactive organometallic reagents are often incompatible with reactive functional groups; however, remarkably, the chemoselectivity was excellent in this case. Imines containing vinyl, ester, and cyano moieties on the aromatic ring underwent the addition reaction to give the corresponding products **5l–n** in very good yields with excellent enantioselectivity. Furthermore, the S-, O-, and N-containing heteroaromatic ketimines **4o–q** were also found to be highly suitable substrates for this asymmetric transformation and provided the corresponding addition products **5o–q** in good yields with high enantioselectivity. Finally, we demonstrated that the aromatic ring is not essential for the system, and that addition to vinyl ketimines is feasible, as exemplified by the formation of product **5r**, albeit with lower enantioselectivity (61 % *ee*) and in low yield. However, a π -system does seem to be necessary

for the addition to take place, as addition to dialkyl ketimines was unsuccessful.

Having established the scope of the reaction with respect to the ketimine substrate, we turned to the Grignard reagent. Whereas previously reported addition reactions to ketimines were restricted to methylation and ethylation, our catalytic system enabled the addition of a wider variety of alkyl Grignard reagents. Our methodology enabled the introduction of Grignard reagents of various chain lengths, such as ethyl, hexyl, and isopentyl, in quantitative yield with excellent enantioselectivity (Table 2, entries 1, 2, and 4). Methylmag-

Table 2: Scope of the reaction with respect to the Grignard reagent.

Entry ^[a]	Product	RMgBr	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	5b	MgBr	quant.	97
2	5s	MgBr	quant.	91
3	5t	MgBr	92	28
4 ^[d]	5u	MgBr	99	93
5	5v	MgBr	quant.	91
6	5w	MgBr	36 ^[e]	95
7	5x	MgBr	81	> 99

[a] Reaction conditions: [**4b**] = 0.1 M, 16–20 h. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC on a chiral stationary phase. [d] The reaction was carried out at –78 °C. [e] The low yield is due to impurities present in the Grignard reagent.

nesium bromide, unfortunately, gave the racemic addition product. An increase in steric hindrance owing to branching posed a problem and led to the formation of the product in nearly racemic form when α -branched Grignard reagents were used and with low enantioselectivity with β -branched Grignard reagents (entry 3). Functionalized Grignard reagents, which provide a handle for future transformations, can be introduced with excellent enantioselectivity, as demonstrated by the reactions in entries 5 and 6 of Table 2. Finally, phenylethylmagnesium bromide was added smoothly to yield the product in nearly enantiomerically pure form (> 99 % *ee*; Table 2, entry 7).

The robustness of the methodology was further evaluated with the following experiments: The reaction for the synthesis of **5b** was scaled up 40-fold (4 mmol, 1 g) without a change in the reaction outcome (99 % yield, 96 % *ee*). The copper-ligand complex could be recovered in 91 % yield and used in a subsequent reaction, which gave the product in quantitative yield with 95 % *ee*. Finally, the catalyst loading could be reduced from 5 to 1 mol% without compromising the yield and with only a small decrease in the enantioselectivity (93 % *ee*).

In summary, we have developed the first asymmetric addition of Grignard reagents to enolizable ketimines. The high reactivity of Grignard reagents has been exploited to tackle the low reactivity of the ketimines. Remarkably, all competing reaction pathways, including substrate enolization, substrate reduction through β -hydride transfer, and non-catalyzed addition (commonly observed with Grignard reagents), could be avoided by the use of a highly chemoselective chiral copper–phosphine catalyst system.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkylation · asymmetric catalysis · copper catalysis · enolizable ketimines · Grignard reagents

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- [12] This hypothesis also correlates with the fact that the reaction mixtures derived from the addition of Grignard reagents to ketimines **1b–d** were heterogeneous, as opposed to those derived from additions to **4a–o**.
- [13] CCDC 1509347 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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