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Copper-catalyzed asymmetric 1,4-conjugate addition of Grignard reagents to linear α,β,γ,δ-unsaturated ketones†

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A highly regioselective and enantioselective copper-catalyzed 1,4-conjugate addition of Grignard reagents to linear α,β,γ,δ-unsaturated ketones was developed. The 1,4-addition products were obtained regioselectively in high yields with up to 98% ee.

Conjugate addition (CA) as a practical and efficient strategy to construct carbon–carbon bonds is of great interest.[1] Controlling the regio- and stereo-selectivity of a reaction is a significant challenge in organic synthesis, especially in asymmetric conjugate additions (ACA). Excellent regio- and stereo-selectivity have been achieved in reactions involving transition metal-catalyzed α,β-unsaturated Michael acceptors.[2] However, due to an additional electrophilic site, the use of α,β,γ,δ-unsaturated Michael acceptors in asymmetric reactions remains a challenge and investigations are currently ongoing to control the formation of specific regioisomers (1,2-, 1,4-, as well as 1,6-products) with high enantioselectivity.[3–8]

Over the past few years, Hayashi *et al.* have developed several successful examples of rhodium- and iridium-catalyzed 1,6-ACAs to both cyclic and linear α,β,γ,δ-unsaturated compounds, utilizing arylnucleophiles.[4] More recently, the same group also reported the cobalt-catalyzed 1,6-ACA of (triisopropylsilyl)-acetylene to α,β,γ,δ-unsaturated carbonyl compounds.[5] The copper-catalyzed ACA of alkyl Grignard and organozinc reagents to α,β,γ,δ-unsaturated compounds has found use in a wide variety of applications. Fillion *et al.*,[6] Feringa *et al.*[7] and Alexakis *et al.*[8] have reported successful reactions involving this type of 1,6-ACA. However, only two examples of copper-catalyzed 1,4-ACA reactions involving α,β,γ,δ-unsaturated compounds have been reported by Alexakis. One method concerns the copper-catalyzed ACA of trialkylaluminum reagents to linear nitrodienes and nitroenynes producing 1,4- or 1,6-products (with up to 95% ee and 91% ee respectively).[8b] Another methodology concerns a copper-catalyzed 1,4-ACA of Grignard reagents to α,β,γ,δ-unsaturated cyclic enones.[9] These two promising results are derived from the specific structural features of the substrates. Highly regioselective and enantioselective 1,4-ACA reactions of linear α,β,γ,δ-unsaturated ketones, the products of which can be readily transformed into important intermediates of peptide isosteres,[10–12] are yet to be reported. Herein we report the first copper-catalyzed ACA of simple alkyl Grignard reagents to linear α,β,γ,δ-unsaturated ketones, exclusively providing the single 1,4-product.[5]

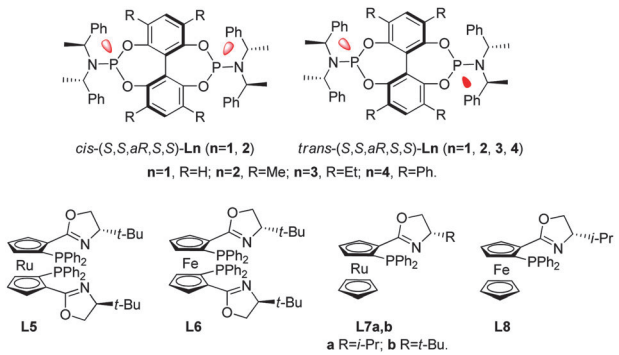

Fig. 1 Chiral ligands used in this work.

A series of phosphoramidite ligands bearing a D_2-symmetric biphenyl backbone (Fig. 1, **L1–L4**) were first employed because of their excellent performance in previous 1,4-ACA reactions reported by our group.[13] After preliminary studies optimizing the reaction conditions, it was found that the conjugate addition of 1.5 equiv. EtMgBr to (2*E*,4*E*)-1,5-diphenyl-2,4-pentadien-1-one (**1a**) was successful in DCM at −70 °C using a 3 mol% Cu–**L1–4** catalyst system (Table 1, entries 1–5). Remarkably, a completely 1,4-selective product was obtained, albeit with low enantioselectivities and moderate yields. No 1,2- or 1,6-products were formed.

In order to develop a more effective catalytic system, chiral metallocene-based phosphinooxazoline ligands[14] were employed in the reaction. To our delight, using chiral P,N-metallocene catalysts, 1,4-products were obtained exclusively with improved yield and enantioselectivity. Using monophosphinooxazoline ligands (entries 8–10) improved catalytic behavior compared to the bis-(phosphinooxazoline) ligands (entries 6 and 7). The substituent

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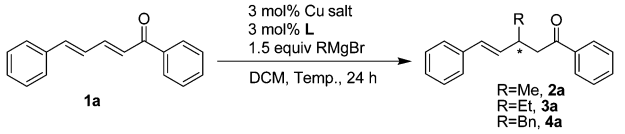
Table 1 Optimizing reaction conditions



Entry	L	R	Cu salt	Temp. (°C)	Yield[a] (%)	ee[b] (%)
1	*cis*-**L1**	Et	Cu(I)(MeCN)$_4$ClO$_4$	−70	72 (**3a**)	17
2	*trans*-**L1**	Et	Cu(I)(MeCN)$_4$ClO$_4$	−70	73 (**3a**)	−8
3	*trans*-**L2**	Et	Cu(I)(MeCN)$_4$ClO$_4$	−70	76 (**3a**)	28
4	*trans*-**L3**	Et	Cu(I)(MeCN)$_4$ClO$_4$	−70	71 (**3a**)	5
5	*trans*-**L4**	Et	Cu(I)(MeCN)$_4$ClO$_4$	−70	31 (**3a**)	0
6	**L5**	Et	Cu(I)(MeCN)$_4$ClO$_4$	−70	76 (**3a**)	12
7	**L6**	Et	Cu(I)(MeCN)$_4$ClO$_4$	−70	56 (**3a**)	4
8	**L7a**	Et	Cu(I)(MeCN)$_4$ClO$_4$	−70	81 (**3a**)	54
9	**L7b**	Et	Cu(I)(MeCN)$_4$ClO$_4$	−70	86 (**3a**)	53
10	**L8**	Et	Cu(I)(MeCN)$_4$ClO$_4$	−70	77 (**3a**)	66
11	**L8**	Me	Cu(I)(MeCN)$_4$ClO$_4$	−70	86 (**2a**)	94
12	**L8**	Bn	Cu(I)(MeCN)$_4$ClO$_4$	−70	40 (**4a**)	4
13	**L8**	Me	Cu(I)TC	−70	78 (**2a**)	92
14	**L8**	Me	Cu(I)(C$_6$H$_6$)OTf	−70	84 (**2a**)	93
15	**L8**	Me	Cu(II)(OAc)$_2$·H$_2$O	−70	75 (**2a**)	91
16	**L8**	Me	Cu(II)(Me$_3$CCO$_2$)$_2$	−70	88 (**2a**)	90
17	**L8**	Me	Cu(II)(acac)$_2$	−70	84 (**2a**)	89
18	**L8**	Me	Cu(II)(OTf)$_2$	−70	83 (**2a**)	80
19	**L8**	Me	Cu(I)(MeCN)$_4$ClO$_4$	−60	79 (**2a**)	78
20[c]	**L8**	Me	Cu(I)(MeCN)$_4$ClO$_4$	−80	67 (**2a**)	97

[a] Yield of the isolated product. [b] Determined by HPLC, Chiralcel AD-H column. [c] The reaction was stirred for 72 h.

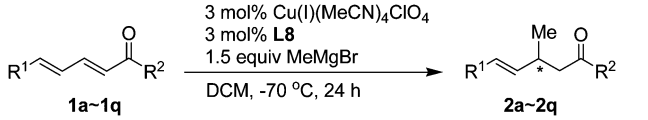
attached to the oxazoline ring of the ruthenocene-based ligands had little effect on enantioselectivity. The use of ferrocene-based ligand **L8** possessing an i-Pr group gave the desired product with an ee of 66% (entry 10). **L8** was thus chosen as the chiral ligand for subsequent reactions.

Using the chosen ligand **L8**, three general Grignard reagents were screened (entries 10–12). It was found that the Grignard reagent had a great effect on enantioselectivity as well as on yield. As the steric hindrance of the Grignard reagent was increased, enantioselectivity and yield decreased. When methyl Grignard was used, the reaction proceeded with 86% yield and 94% ee (entry 11). The effects of copper salts on the reaction were next examined (entries 11 and 13–18). Cu(I)(MeCN)$_4$ClO$_4$ provided the most satisfactory result (entry 11). Different temperatures were then screened in this asymmetric 1,4-conjugate addition to optimize the reaction conditions (entries 11, 19 and 20). Increasing the temperature of the reaction to −60 °C gave moderate enantioselectivity (entry 19). The highest enantioselectivity was observed at −80 °C, but the product was only obtained in 67% yield after 72 h (entry 20).

With the optimized reaction conditions in hand, substrate scope was investigated using Cu(I)(MeCN)$_4$ClO$_4$–**L8** as a catalytic system in DCM at −70 °C. The results are shown in Table 2.

To test the effect of steric hindrance on the reaction outcome, we introduced a methyl group at the *ortho*-, *meta*- and *para*-positions (R^1 and R^2) of the phenyl groups of substrate **1** (entries 1–4 and 8–10). **1b** (R^1 = *o*-MeC$_6$H$_4$) and **1i** (R^2 = *m*-MeC$_6$H$_4$) gave their corresponding products with 94% ee and 92% ee respectively (entries 2 and 9). When an electron-donating methoxy group was introduced at the *para*-position of the phenyl ring R^1, enantioselectivity decreased (entry 5). However, addition of an electron-withdrawing substituent was beneficial to this reaction. Electron-withdrawing groups such as chloro or trifluoromethyl

Table 2 Substrate scope



Entry	Substrate	R^1	R^2	Yield[a] (%)	ee[b] (%)
1	**1a**	Ph	Ph	86 (**2a**)	94
2	**1b**	*o*-MeC$_6$H$_4$	Ph	84 (**2b**)	94
3	**1c**	*m*-MeC$_6$H4	Ph	82 (**2c**)	87
4	**1d**	*p*-MeC$_6$H$_4$	Ph	90 (**2d**)	76
5	**1e**	*p*-MeOC$_6$H$_4$	Ph	85 (**2e**)	83
6	**1f**	*o*-ClC$_6$H$_4$	Ph	83 (**2f**)	96
7[c]	**1g**	*p*-ClC$_6$H$_4$	Ph	86 (**2g**)	97
8	**1h**	Ph	*o*-MeC$_6$H$_4$	73 (**2h**)	36
9	**1i**	Ph	*m*-MeC$_6$H$_4$	84 (**2i**)	92
10	**1j**	Ph	*p*-MeC$_6$H$_4$	87 (**2j**)	82
11	**1k**	Ph	*m*-ClC$_6$H$_4$	80 (**2k**)	96
12[c]	**1l**	Ph	*p*-ClC$_6$H$_4$	88 (**2l**)	97
13[c]	**1m**	Ph	*p*-CF$_3$C$_6$H$_4$	92 (**2m**)	95
14	**1n**	Ph	2-Naphthyl	70 (**2n**)	83
15	**1o**	*p*-ClC$_6$H$_4$	*p*-ClC$_6$H$_4$	92 (**2o**)	98
16	**1p**	Ph	2-Thienyl	69 (**2p**)	62
17	**1q**	Ph	2-Furyl	86 (**2q**)	89

[a] Yield of the isolated product. [b] Determined by HPLC, Chiralcel AD-H column. [c] The reaction was stirred at −60 °C for 24 h.

substituents displayed excellent enantioselectivity, irrespective of their position being *ortho*, *meta* or *para* (entries 6–7 and 11–13). Replacing the phenyl ring R^2 with a 2-naphthyl group gave the desired product with 83% ee (entry 14). A *para*-chloro group on the phenyl ring R^1 and R^2 provided the best results, with products being obtained with 98% ee (entry 15). To expand the range of the substrates, compounds containing heterocycles such as thienyl and furyl rings were also employed in this reaction, which proceeded with moderate to excellent enantioselectivities (up to 89% ee, entries 16 and 17). When R^2 was replaced by a methyl group, the reaction occurred *via* a 1,2-addition, affording a racemic product in 81% yield with no formation of the 1,4-addition product.

A single crystal X-ray structure of **2a** (Fig. 2) was obtained, which indicated that **2a** was the 1,4-product with *R* absolute configuration.[15] The catalytic cycle for the 1,4-ACA reaction can thus be proposed (Scheme 1). The Cu–ligand complex A forms a π complex B with MeMgBr and substrate **1a**. The Cu(III) σ complex C is formed *via* oxidative addition, which is stabilized by the diconjugated system. This accounts for the preference of the 1,4-selectivity over 1,6-selectivity.[7a] Reductive elimination of C occurs to give complex A and the 1,4-product D. The enantioselectivity can be explained using the mechanism reported by Feringa's group involving the 1,4-ACA of Grignard reagents.[16]

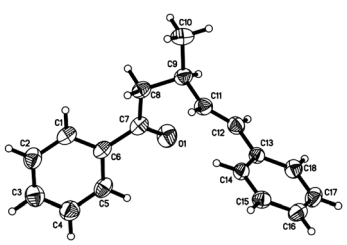
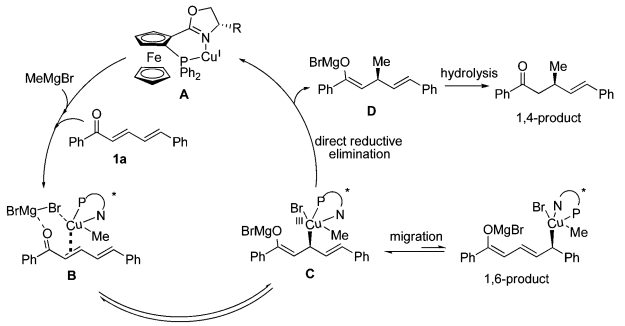
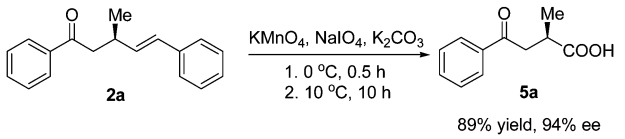


Fig. 2 X-ray structure of **2a**.



Scheme 1 A proposed catalytic cycle.



Scheme 2 Synthesis of chiral 2-substituted-γ-keto acid from **2a**.

The (*R*)-1,4-product, γ,δ-unsaturated ketone **2a**, provides access to a simple synthesis of important chiral 2-substituted-γ-keto acid intermediates.[11] These intermediates are useful for the preparation of peptide mimetics (peptide isosteres) in drug discovery. For example, they can be used for the synthesis of human neutrophile elastase inhibitors[12] and angiotensin converting enzyme inhibitors.[13] 2-Substituted-γ-keto acids **5a** can be prepared as shown in Scheme 2 in 89% yield with 94% ee.

In summary, we have developed a new method for highly regio- and enantio-selective copper-catalyzed asymmetric 1,4-conjugate addition reactions of Grignard reagents to α,β,γ,δ-unsaturated ketones, using 1,2-disubstituted planar chiral ferrocene-based phosphinooxazoline ligands. A series of γ,δ-unsaturated ketones **2** were obtained in high yields and with high enantioselectivity (up to 98% ee and 92% yield). The products could be readily converted to important intermediates such as chiral 2-substituted-γ-keto acids.

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Notes and references

1 P. Perlmutter, *Conjugate Addition Reactionsin Organic Synthesis*, Pergamon, Oxford, 1992.
2 Reviews on 1,4-ACA, see: (*a*) K. Tomioka and Y. Nagaoka, *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, New York, 1999, vol. 3, p. 1105; (*b*) B. L. Feringa, *Acc. Chem. Res.*, 2000, **33**, 346; (*c*) T. Hayashi, *Acc. Chem. Res.*, 2000, **33**, 354; (*d*) N. Krause and A. Hoffmann-Röder, *Synthesis*, 2001, 171; (*e*) A. Alexakis and C. Benhaim, *Eur. J. Org. Chem.*, 2002, **19**, 3221; (*f*) B. L. Feringa, R. Naasz, R. Imbos and L. A. Arnold, *Modern Organocopper Chemistry*, ed. N. Krause, Wiley-VCH, Weinheim, 2002, p. 224; (*g*) K. Yamasaki and T. Hayashi, *Chem. Rev.*, 2003, **103**, 2829; (*h*) F. López, A. J. Minnaard and B. L. Feringa, *Acc. Chem. Res.*, 2007, **40**, 179; (*i*) J. Christoffers, G. Koripelly, A. Rosiak and M. Rössle, *Synthesis*, 2007, 1279; (*j*) A. Alexakis, J. E. Backvall, N. Krause, O. Pamies and M. Dieguez, *Chem. Rev.*, 2008, **108**, 2796; (*k*) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824; (*l*) J. F. Teichert and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2010, **49**, 2486.
3 Reviews on 1,6-CA: (*a*) J. W. Ralls, *Chem. Rev.*, 1959, **59**, 329; (*b*) Y. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 947; (*c*) N. Krause and A. Gerold, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 186; (*d*) M. A. Frederik and M. Hulce, *Tetrahedron*, 1997, **53**, 10197; (*e*) N. Krause and S. Thorand, *Inorg. Chim. Acta*, 1999, **296**, 1; (*f*) A. G. Csák, G. Herrán and M. C. Murcia, *Chem. Soc. Rev.*, 2010, **39**, 4080; (*g*) E. M. P. Silva and A. M. S. Silva, *Synthesis*, 2012, 3109.
4 (*a*) T. Hayashi, N. Tokunaga and K. Inoue, *Org. Lett.*, 2004, **6**, 305; (*b*) T. Hayashi, S. Yamamoto and N. Tokunaga, *Angew. Chem., Int. Ed.*, 2005, **44**, 4224; (*c*) T. Nishimura, Y. Yasuhara, T. Sawano and T. Hayashi, *J. Am. Chem. Soc.*, 2010, **132**, 7872; (*d*) T. Nishimura, H. Makino, M. Nagaosa and T. Hayashi, *J. Am. Chem. Soc.*, 2010, **132**, 12865; (*e*) T. Nishimura, A. Noishiki and T. Hayashi, *Chem. Commun.*, 2012, **48**, 973.
5 T. Sawano, A. Ashouri, T. Nishimura and T. Hayashi, *J. Am. Chem. Soc.*, 2012, **134**, 18936.
6 E. Fillion, A. Wilsily and E. T. Liao, *Tetrahedron: Asymmetry*, 2006, **17**, 2957.
7 (*a*) T. den Hartog, S. R. Harutyunyan, D. Font, A. J. Minnaard and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2008, **47**, 398; (*b*) T. den Hartog, D. J. van Dijken, A. J. Minnaard and B. L. Feringa, *Tetrahedron: Asymmetry*, 2010, **21**, 1574.
8 (*a*) H. Henon, M. Mauduit and A. Alexakis, *Angew. Chem., Int. Ed.*, 2008, **47**, 9122; (*b*) M. Tissot, D. Muller, S. Belot and A. Alexakis, *Org. Lett.*, 2010, **12**, 2770; (*c*) J. Wencel-Delord, A. Alexakis, C. Crevisy and M. Mauduit, *Org. Lett.*, 2010, **12**, 4335.
9 M. Tissot, D. Poggiali, H. Henon, D. Muller, L. Guenee, M. Mauduit and A. Alexakis, *Chem.–Eur. J.*, 2012, **18**, 8731.
10 (*a*) E. Nakamura, K. Sekiya and I. Kuwajima, *Tetrahedron Lett.*, 1987, **28**, 337; (*b*) R. V. Hoffman and H. O. Kim, *Tetrahedron Lett.*, 1993, **34**, 2051; (*c*) T. Noguchi, A. Onodera, K. Tomisawa, M. Yamashita, K. Takeshita and S. Yokomori, *Bioorg. Med. Chem.*, 2002, **10**, 2713; (*d*) F. Zhang and E. J. Corey, *Org. Lett.*, 2004, **6**, 3397.
11 R. J. Cregge, S. L. Durham, R. A. Farr, S. L. Gallion, C. M. Hare, R. V. Hoffman, M. J. Janusz, H. O. Kim, J. R. Koehl, S. Mehdi, W. A. Metz, N. P. Peet, J. T. Pelton, H. A. Schreuder, S. Sunder and C. Tardif, *J. Med. Chem.*, 1998, **41**, 2461.
12 F. J. McEvoy, F. M. Lai and J. D. Albright, *J. Med. Chem.*, 1983, **26**, 381.
13 (*a*) H. Zhang, F. Fang, F. Xie, H. Yu, G. Yang and W. Zhang, *Tetrahedron Lett.*, 2010, **51**, 3119; (*b*) F. Fang, H. Zhang, F. Xie, G. Yang and W. Zhang, *Tetrahedron*, 2010, **66**, 3593; (*c*) B. Yang, F. Xie, H. Yu, K. Shen, Z. Ma and W. Zhang, *Tetrahedron*, 2011, **67**, 6197; (*d*) H. Yu, F. Xie, Z. Ma, Y. Liu and W. Zhang, *Adv. Synth. Catal.*, 2012, **68**, 1941; (*e*) H. Yu, F. Xie, Z. Ma, Y. Liu and W. Zhang, *Org. Biomol. Chem.*, 2012, **10**, 5137.
14 For planar chiral ferocene-based phosphinooxazoline ligands, see: (*a*) C. J. Richards, T. Damalidis, D. E. Hibbs and M. B. Hursthouse, *Synlett*, 1995, 74; (*b*) Y. Nishibayashi and S. Uemura, *Synlett*, 1995, 79; (*c*) W. Zhang, Y. Adachi, T. Hirao and I. Ikeda, *Tetrahedron: Asymmetry*, 1996, **7**, 451; (*d*) W. Zhang, T. Hirao and I. Ikeda, *Tetrahedron Lett.*, 1996, **37**, 4545; (*e*) T. Sammakia and E. L. Stangeland, *J. Org. Chem.*, 1997, **62**, 6104. For planar chiral ruthenocene-based phosphino-oxazoline ligands, see: (*f*) D. Liu, F. Xie and W. Zhang, *Tetrahedron Lett.*, 2007, **48**, 585; (*g*) D. Liu, F. Xie and W. Zhang, *J. Org. Chem.*, 2007, **72**, 6992; (*h*) D. Liu, F. Xie, X. Zhao and W. Zhang, *Tetrahedron*, 2008, **64**, 3561; (*i*) Y. Wang, D. Liu, Q. Meng and W. Zhang, *Tetrahedron: Asymmetry*, 2009, **20**, 2510; (*j*) H. Guo, D. Liu, N. Butt, Y. Liu and W. Zhang, *Tetrahedron*, 2012, **68**, 3295.
15 CCDC 930399†.
16 S. R. Harutyunyan, F. López, W. R. Browne, A. Correa, D. Peña, R. Badorrey, A. Meetsma, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2006, **128**, 9103.

