Homogeneous Catalysis

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Iron-Catalyst-Switched Selective Conjugate Addition of Grignard Reagents: α,β,γ,δ-Unsaturated Amides as Versatile Templates for Asymmetric Three-Component Coupling Processes**

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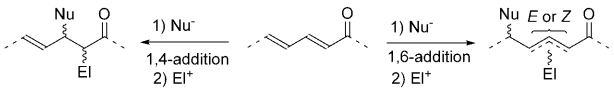
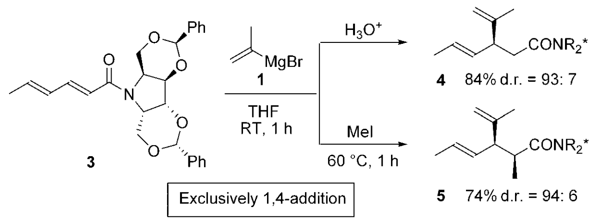
Conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds is one of the most fundamental methods for carbon–carbon bond formation and is usually carried out with copper catalysis.[1,2] Among the various kinds of carbonyl compounds employed for this procedure, dienic substrates have not been amply investigated, presumably as a result of the accumulated difficulties in controlling both regio- and stereoselections, as shown in Scheme 1.[3,4] We report herein that α,β,γ,δ-unsaturated amides work as a simple yet versatile template to circumvent this problem, where the absence or presence of an iron catalyst, rather than the aforementioned copper catalyst, is another key to achieving clear-cut reactions.



Scheme 1. Conjugate addition to dienic carbonyl compounds.

While 1,4-regioselective addition of Grignard reagents to α,β,γ,δ-unsaturated amides was documented almost twenty-five years ago, we revisited this reaction using (*E*,*E*)-*N*,*N*-diethyl-2,4-hexadienamide as a dienic substrate.[5] After surveying various Grignard reagents, we found that using isopropenylmagnesium bromide (**1**) results in an excellent 1,4-:1,6-selectivity of 94:6 in THF without any other additive(s) to give (*E*)-*N*,*N*-diethyl-3-isopropenyl-4-hexenamide (**2**) in a synthetically acceptable 65% yield. This result allowed us to explore asymmetric 1,4-addition by using a chiral amide group.[6] Among several such candidates,[7] amide **3**, incorporating a sugar-derived pyrrolidine unit (Scheme 2),[8] showed exclusive 1,4-regioselectivity and satisfactory product yield (**4**, 84%), both of which were more enhanced than those of **2**, probably as a result of the ether functionality present in the chiral auxiliary (see below). We also found that conjugate addition was highly stereoselective, giving **4** in 93:7 diastereoselectivity. More importantly, the subsequent alkylation of the resultant enolate also proceeded in a highly stereoselective manner to give **5** (Scheme 2), which consists of a 94:6 mixture of two major diastereoisomers with two other isomers being formed in trace amounts.[9,10] This ratio (94:6) reflects that of the addition product **4** (93:7), thus suggesting that the stereochemistry of methylation is perfectly controlled by the proximate chiral amide auxiliary, which is further evidenced by the fact that the isomeric ratio of **5** did not change after the removal of amide auxiliary, as shown in Equation (1).



Scheme 2. 1,4-Addition of Grignard reagent and successive alkylation.

Scheme 3 illustrates a proposed reaction course. The reaction should proceed via a less hindered conformation **3** (rather than **3′**), in which the reacting Grignard reagent **1** is fixed at the depicted position in **6** by the chelation of magnesium to the carbonyl and acetal oxygen atoms. From the intermediate **6**, the alkenyl (R) group migrates to the diene carbon β to the carbonyl group, to account for the higher 1,4-selectivity and better product yield (of **4**) than for the simple diethylamide **2**. In addition, alkylation of the resulting enolate **7** most likely proceeds from the side where the magnesium coordinates (as in **8**), to produce **5**.

Results for the above three-component coupling process, incorporating different amides, Grignard reagents, and organic halides, are listed in Table 1. The chiral enolate generated by the 1,4-addition was alkylated with activated halides, such as methyl iodide, allyl bromide, propargyl

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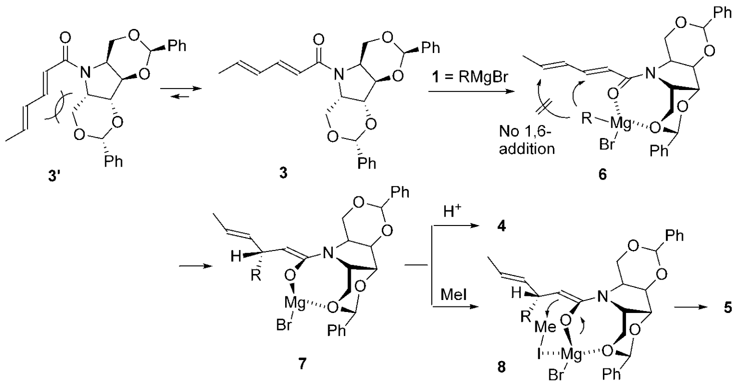
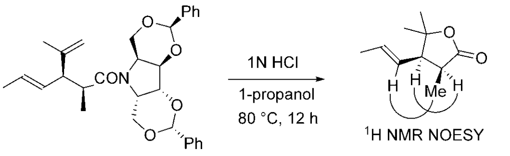


Scheme 3. Proposed reaction course for 1,4-addition.

bromide, and benzyl bromide (other than entry 4), and also a less reactive primary-alkyl iodide (Table 1, entry 4) in good yields with exclusive regioselectivity and excellent diastereoselectivities.[10] α-Hexyl- and α-silylvinyl Grignard reagents also gave the products **12** and **13** with high asymmetric induction (Table 1, entries 5 and 6). Variation in the amide substrates (**14**–**16**) further illustrated the synthetic flexibility of this method (Table 1, entries 7–9).

The chiral auxiliary in **5** was readily removed by acidic hydrolysis, as shown in Equation (1),[11] to give lactone **20**, which has thermodynamically less stable *cis*-substituents on its five-membered ring. This stereochemical outcome and the separately confirmed structure of **4** were used to assign the depicted absolute stereochemistry to **5**.



5 d.r. = 94 : 6   **20** 71% d.r. = 94 : 6   (1)

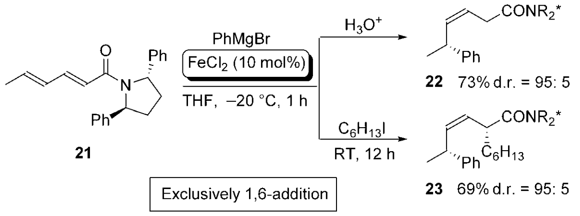
Table 1: Three-component coupling process based on 1,4-addition of Grignard reagents according to Scheme 2.[a]

Entry	Substrate	Grignard Reagent	Alkylation	Product[b]	Yield [%][c]	d.r.[d]
1	$CONR_2$* **3**	MgBr	MeI	$CONR_2$* **5**	74	94:6
2	**3**	MgBr	Br (allyl)	$CONR_2$* **9**	66	95:5
3	**3**	MgBr	Br (propargyl)	$CONR_2$* **10**	44	94:6
4	**3**	MgBr	$C_6H_{13}I$	$CONR_2$*, C_6H_{13} **11**	62	94:6
5	**3**	$SiMe_3$ MgBr	MeI	$SiMe_3$ $CONR_2$* **12**	73	92:8
6	**3**	C_6H_{13} MgBr	MeI	C_6H_{13} $CONR_2$* **13**	53	97:3
7[e]	Pr $CONR_2$* **14**	MgBr	BnBr[f]	Pr $CONR_2$* Ph **17**	65	94:6
8[e]	Me_3Si $CONR_2$* **15**	MgBr	MeI	Me_3Si $CONR_2$* **18**	76	95:5
9[e]	$CONR_2$* **16**	MgBr	MeI	$CONR_2$* **19**	87	93:7

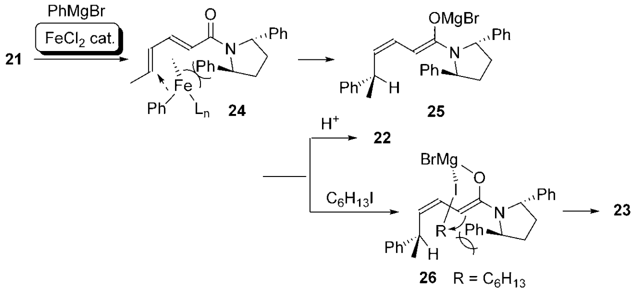
[a] Molar ratio: dienamide/Grignard reagent/alkylating agent = 1:2:4. [b] The most abundant diastereoisomer is depicted. Absolute stereochemistries of **9**–**13** and **17**–**19** were deduced based on that of **5** by analogy. [c] Yields that are not necessarily optimized. [d] The ratio of two major diastereoisomers. Two other isomers, which were formed in less than trace amounts and could not be isolated nor characterized, are omitted. [e] NR_2* is the same as that in **3**. [f] Alkylation was performed at room temperature for 12 h.

Regio- and stereoselective 1,6-addition of Grignard reagents to α,β,γ,δ-unsaturated amides is complementary to the above 1,4-addition as illustrated in Scheme 1. While we reported that the exclusive 1,6-selective addition of aryl Grignard reagents to α,β,γ,δ-unsaturated esters and amides was viable with an iron catalyst,[12–15] the remote asymmetric induction from a chiral amide portion to the carbon δ to the carbonyl, which is categorized as 1,7-chirality transfer,[16] appeared quite difficult. Nonetheless, of the chiral esters and amides tested,[17] amide **21**[18] (see Scheme 4) was most promising. The iron-catalyzed 1,6-addition of PhMgBr to **21** proceeded with exclusive regioselectivity and high diastereoselectivity to give **22**, or the same addition followed by the stereoselective alkylation of the resulting enolate gave **23** as a 95:5 mixture of two (of a possible four) diastereoisomers.

In these products, the amide moiety and the incoming aryl group are *cis* to each other about the carbon–carbon double bond, which suggests that the reaction most likely proceeds via the *s-cis*-diene iron complex **24**[12,19] to generate **25** (and subsequently **22** or **23**) as shown in Scheme 5. This olefin geometry is in stark contrast to that



Scheme 4. Iron-catalyzed 1,6-addition and successive alkylation.



Scheme 5. Proposed reaction course for 1,6-addition. L_n = ligands.

in copper-catalyzed reactions, where the carbonyl and the introduced alkyl groups are usually *trans*.[4a–c,f,g] The same intermediate **24** could account for the anomalously high level of 1,7-chirality transfer, because the amide auxiliary efficiently blocks one plane of the *s-cis*-diene, whereas the iron complexation takes place from another side (**21**→**24**, Scheme 5) to promote efficient asymmetric delivery of the Ph group (**24**→**25**), which is followed by highly stereoselective alkylation (**26**→**23**). Thus, throughout the reaction, the iron catalyst should play three roles; to control 1) the regiochemistry of the conjugate addition, 2) the olefinic geometry of the product, and 3) the efficient remote chiral induction.

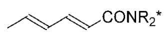
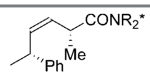
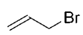
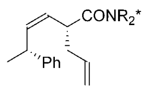
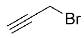
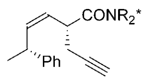
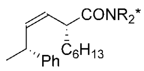
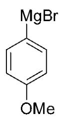
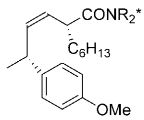
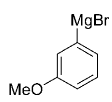
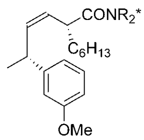
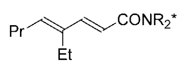
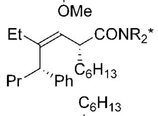
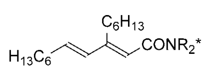
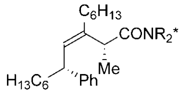
Table 2 shows the generality of this reaction. The 1,6-addition and the subsequent alkylation of **21** could be carried out with a variety of aryl Grignard reagents and alkylating agents to produce the desired products, **23** and **27**–**31** (Table 2, entries 1–6). The same reaction sequence with differently substituted amides **32** and **33** gave the products **34** and **35**, in very high diasteromeric ratios, without any complication (Table 2, entries 7 and 8).

In conclusion, switching between exclusive 1,4- and 1,6-additions of Grignard reagents to α,β,γ,δ-unsaturated amides is now possible, owing to the absence or presence of an iron catalyst. Moreover, α,β,γ,δ-unsaturated amides can be utilized as a simple yet versatile template for asymmetric three-component coupling process by the present one-pot reaction.

Experimental Section

(2*S*,3*R*,*E*)-2-Methyl-3-(1-methylethenyl)-4-hexenamide (**5**, derived from 1,3:4,6-di-*O*-benzylidene-2,5-dideoxy-2,5-imino-L-iditol): isopropenylmagnesium bromide (**1**) (0.53 M in THF, 0.377 mL, 0.200 mmol) was added to a stirred solution of **3** (43.4 mg, 0.100 mmol, ca. 100 % *ee*) in THF (2.0 mL) at –20 °C under argon. The solution was rapidly warmed to room temperature and was stirred at the same temperature for 1 h. Iodomethane (0.025 mL, 0.400 mmol) was added to this solution at room temperature, and the solution was stirred at 60 °C for 1 h. The reaction was cooled to room temperature and was terminated by the addition of an aqueous saturated NH_4Cl solution (2.0 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo to give a crude oil, which was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford **5** (36.5 mg, 74 %) as a white solid. ^{1}H NMR spectroscopic analysis of isolated **5** revealed that the diastereoselectivity was 94:6, which is comparable to the value detected at the crude stage.

Table 2: Three-component coupling process based on the iron-catalyzed 1,6-addition according to Scheme 4.[a]

Entry	Substrate		ArMgBr	Alkylation	Product[b]		Yield [%][c]	d.r.[d]
1		21	PhMgBr	MeI		27	67	95:5
2	21		PhMgBr			28	58	95:5
3	21		PhMgBr			29	55	94:6
4	21		PhMgBr	$C_6H_{13}I$		23	69	95:5
5	21			$C_6H_{13}I$		30	63	96:4
6	21			$C_6H_{13}I$		31	70	94:6
7[e]		32	PhMgBr	$C_6H_{13}I$		34	71	96:4
8[e]		33	PhMgBr	MeI[f]		35	68	97:3

[a] Molar ratio: dienamide/$FeCl_2$/ArMgBr/alkylating agent = 1:0.1:2.5:5. [b] The most abundant diastereoisomer is depicted. Absolute stereochemistries of **27**–**31**, **34** and **35** were deduced by analogy based on that of **23**. [c] Yields that are not necessarily optimized. [d] The ratio of two major diastereoisomers. Two other isomers, which were formed in trace amounts and could not be isolated or characterized, are omitted. [e] NR_2* is the same as that in **21**. [f] Alkylation was performed at 0 °C for 12 h.

(2*R*,5*R*,*Z*)-*N*,*N*-[(1′*S*,4′*S*)-1′,4′-Diphenyl-1′,4′-butylidene]-2-hexyl-5-phenyl-3-hexenamide (**23**): PhMgBr (1.0 M in THF, 0.250 mL, 0.250 mmol) was added over 7 min to a stirred solution of **21** (31.7 mg, 0.100 mmol, 97% *ee*[20]) and $FeCl_2$ (1.3 mg, 0.010 mmol) in THF (1.0 mL) in a 30 mL round-bottomed flask at −20°C under argon to give a dark brown to black homogeneous solution. After the solution was stirred at the same temperature for 1 h, 1-iodohexane (0.074 mL, 0.500 mmol) was added. The solution was warmed to room temperature and stirred for 12 h. The reaction was terminated by the addition of 1M aqueous HCl (1.0 mL) at room temperature. The reaction mixture was diluted with ethyl acetate and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with an aqueous saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated in vacuo to give a crude oil, ^{1}H NMR spectroscopic analysis of which revealed that the diastereoselectivity was 95:5 and that the regio- and olefinic stereoisomers were absent. The product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford **23** (33.3 mg, 69%) as a white solid, having the same isomeric composition as above.

Products **5** and **23** were fully characterized by ^{1}H NMR, ^{13}C NMR spectroscopy, IR, elemental analyses, and appropriate derivatizations. Their spectroscopic data and detailed structural determinations are shown in the Supporting Information.

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Keywords: amides · asymmetric reaction · conjugate addition · Grignard reagents · iron

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[5] Although 1,4-addition of Grignard reagents to α,β,γ,δ-unsaturated amides was reported (reference [3b]), the precise regioselectivities were not described and low to moderate product yields were reported. In our group, among alkyl, alkenyl, and aryl Grignard reagents, only isopropenyl-like reagents proved satisfactory for this study. For Grignard conjugate addition to α,β-unsaturated amides, see reference [1b].

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[7] Similar amides derived from prolinol or α,α-diphenylprolinol and amide **21** showed lower product yields and/or diastereoselectivities.

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