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Oxidative coupling of enolates using memory of chirality: an original enantioselective synthesis of quaternary α-amino acid derivatives†

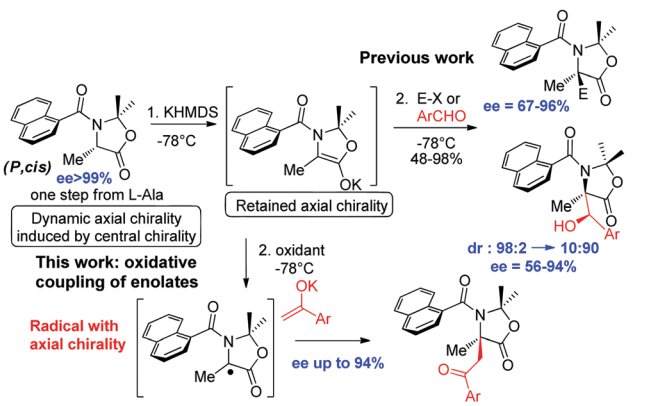
Antonin Mambrini, Didier Gori, Régis Guillot, Cyrille Kouklovsky and Valérie Alezra *

We describe here the first enantioselective oxidative heterocoupling of enolates. Our strategy relies on the memory of chirality concept and allows the stereocontrolled formation of quaternary centres on α-amino acid derivatives with an enantiomeric excess of up to 94%.

Oxidative coupling of enolates[1,2] is a very powerful synthetic method as it enables direct access to 1,4-dicarbonyl compounds, which are not easy to make as their synthesis requires functional group *umpolung* strategies. In recent years, extensive research works have provided several methods for efficient intra[3] and intermolecular oxidative coupling.[4,5] However, most of them are racemic or rely on preexisting stereogenic centers in the enolate precursor as a chiral inducer (diastereoselective oxidative coupling).[6–10] To develop an enantioselective version of this reaction, application of traditional means such as enantioselective catalysis or use of enantiopure stoichiometric reagents seems difficult. There is only one example of enantioselective oxidative homocoupling of a titanium enolate with a chiral ligand but the meso compound is the major product and the enantiomeric excess of the chiral diastereomer is only 76%.[11,12] On the contrary, the memory of chirality (MOC)[13–15] strategy appears to be promising in this context. Indeed, in an MOC reaction, the initial chirality of the starting material is retained during the reaction in the global chiral conformation of the molecule, which should be the case for the generated radical. This strategy has mostly been applied to carbanion intermediates[16–22] but also to carbocations[23,24] or radicals.[25–34] In radical reactions there are only two examples of intermolecular MOC reactions: one recombines 2 radicals in close vicinity,[35] and one uses arene–$Cr(CO)_3$ complexes.[36] Our group has been involved for many years in the development of asymmetric syntheses of quaternary α-amino acids based on the MOC principle. We have thus described efficient intermolecular alkylation or aldol reactions of enolates by memorizing the initial central chirality of a natural tertiary α-amino acid in the axial chirality of tertiary aromatic amides (Scheme 1).[37–40] We wanted to extend our strategy to radical reactions in order to enlarge its scope, our aim being to achieve oxidation of the intermediate enolate into a stabilized captodative radical. In this paper, we report our efforts towards enantioselective oxidative heterocoupling of enolates using memory of chirality and consequently describe the first enantioselective version of this reaction.

We used oxazolidinone **1** derived from L-alanine to screen oxidants. We chose acetophenone as the other partner since deprotonation can occur only on one side and because the electronic character of the enolate is easily tunable by changing the substituents of the aromatic ring. The results for oxidant screening are reported in Table 1.

The most promising results were obtained with Cu(2-ethylhexanoate)$_2$ as an oxidant (entry 1). Several byproducts were



Scheme 1 Alkylation and aldol reaction by MOC and oxidative coupling by MOC.

Faculté des Sciences d'Orsay, Univ. Paris-Sud, Laboratoire de Méthodologie, Synthèse et Molécules Thérapeutiques, ICMMO, UMR 8182, CNRS, Université Paris-Saclay, Bât 410, 91405 Orsay, France. E-mail: valerie.alezra@u-psud.fr

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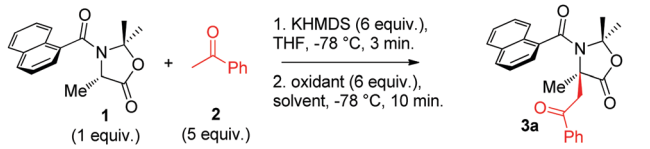
Table 1 Oxidant screening for the enolate coupling between acetophenone and oxazolidinone **1**



Entry	Oxidant	Solvent	Yield (%)	ee[a] (%)
1	Cu(2-ethylhexanoate)$_2$	THF	38	44
2	$CuCl_2$	THF	18	20
3	$Cu(OTf)_2$	THF	0	—
4	Ph_2IOTf	DMF	28	24
5	CAN	DMF	0	—
6	AgOTf	THF	0	—
7[b]	$Mn(acac)_3$	THF	52	4
8	$TiCl_4$	THF	7	40

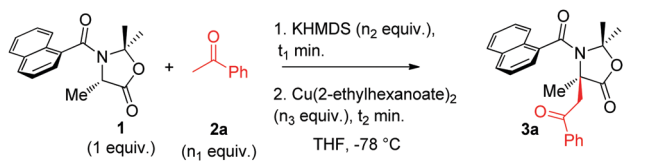
[a] Determined by chiral stationary-phase HPLC. [b] Only 4 equiv. of acetophenone were used.

observed such as those resulting from autocondensation of acetophenone, or oxidative homocoupling of oxazolidinone **1** or of acetophenone. Other oxidants, such as $FeCl_3$, $FeCp_2PF_6$, and I_2, gave either no reaction ($FeCl_3$) or a complex mixture of products. The best results obtained with Cu(2-ethylhexanoate)$_2$ are probably partially due to its good solubility in THF at low temperature.

We then tried to optimize this reaction and modified the reaction conditions (Table 2). We studied the influence of the amounts of acetophenone, base, copper and reaction time, as well as the use of additives.

Although it was previously reported that the aggregation state is sometimes very important to favor heterocoupling *vs.* homocoupling,[41] the presence of additives that dissociate enolate aggregates did not improve the yields or selectivities

Table 2 Optimization of heterocoupling with acetophenone



Entry	Additive[a]	n_1	n_2	t_1 (min)	n_3	t_2 (min)	Yield (%)	ee[b] (%)
1	—	5	7	3	6	10	43	46
2	—	5	6	3	6	10	38	44
3	—	5	6	3	6	3	38	39
4	—	5	6	3	6	30	41	40
5	—	**4**	**6**	**3**	**6**	**30**	**45**	**64**
6[c]	—	4	6	3	6	30	43	62
7	—	4	6	3	4	30	44	65
8	—	4	6	3	3	30	32	62
9	DMPU	4	6	3	3	30	44	62
10	TMEDA	4	6	3	3	30	38	62
11	—	4	6	6	6	30	63	45
12	—	**4**	**10**	**3**	**6**	**30**	**53**	**64**
13	—	3	10	3	4	30	38	60

[a] 2.7 equiv. were added with acetophenone. [b] Determined by chiral stationary-phase HPLC. [c] LDA was used instead of KHMDS.

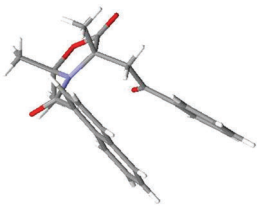
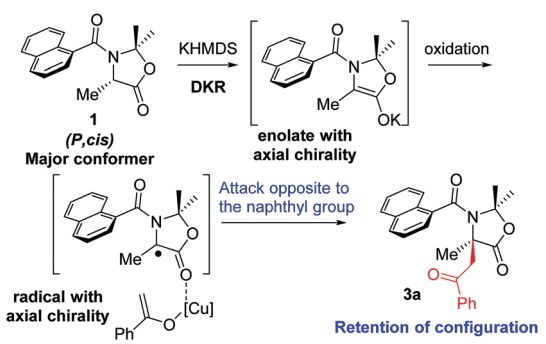


Fig. 1 Crystallographic structure of compound **3a**.

(entries 9 and 10), as well as the replacement of KHMDS by LDA (entries 5 and 6). A decrease of acetophenone improved the enantiomeric excess without modifying the yield (entries 4 and 5). On the contrary, a larger quantity of base improved the yield (entries 1 and 2, or 5 and 12) although using 6 or 10 equivalents of KHMDS gave similar results. Increasing the deprotonation time was beneficial to the yield but induced racemization (entries 5 and 11); in contrast, the oxidation time seemed to have no influence on the reaction (entries 2 to 4).

Compound **3a** was crystalline (Fig. 1), which allowed confirmation of the structure; however the crystal was unfortunately racemic. We thus determined the absolute configuration of compound **3a** by performing alkylation of compound **1** with KHMDS (1.1 equiv.) and bromoacetophenone in THF (see the ESI† for details). The expected compound **3a** was obtained in only 10% yield (the electrophile degrades itself rapidly under these conditions) and 60% ee. As we previously proved that alkylation reactions occurred with a retention of configuration,[39] we were able to compare the HPLC chromatograms and thus confirmed that the major enantiomer issued from enolate oxidative coupling has the same configuration as the one obtained *via* alkylation. Moreover, this experiment showed that in this case, oxidative coupling is much more efficient than alkylation.

This retention of configuration can be explained in the same way as for alkylation:[39] deprotonation occurs preferentially on the major (*P*,*cis*) conformer *via* a dynamic kinetic resolution (DKR), leading to an enolate with an axial chirality, and then to a radical with the same axial chirality; the other partner attacks the radical on its less hindered side, opposite to the naphthyl group leading to global retention of configuration (Scheme 2). Attempts to react the oxazolidinone radical with acetophone trimethylsilyl enol ether failed suggesting that an enolate is



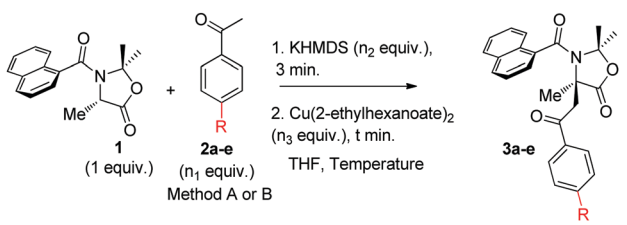
Scheme 2 Explanation of stereoselectivity by MOC.

mandatory, and that there is probably a copper complexation of both intermediates.

We then decided to extend this strategy to substituted acetophenones to explore the influence of the electron density of the aromatic group and to enlarge the scope of this reaction. We also decided to try a protocol with separated deprotonation (method B) to enable the fine tuning of the deprotonation time of compounds **2a**–e. Temperature and oxidation time were also modified in order to improve ees and yields. The results are gathered in Table 3.

Changing temperature from −78 °C to −85 °C has no influence on the reaction. Modifying the deprotonation method (replacing method A with method B) increased in most cases the enantiomeric excess but decreased slightly the yield. On the contrary, this reaction was found to be strongly dependent on the electron density of the aromatic ring: although electron-poor aromatic compounds gave higher yields but lower ees (compare entries 2 and 7 or 8), electron-rich aromatic substrates gave lower yields but higher ees (compare entries 7 and 10). The best ees were thus obtained with 4′-methoxy acetophenone or with 4′-(dimethylamino)acetophenone (71–74%). The yields are moderate but in this kind of oxidative heterocoupling, it is often the case. To explain this link between the yield/enantiomeric excess and the electron-density, we can propose that deprotonation occurs faster on an electron-poor compound such as *para*-nitro acetophenone, but the enolate is either less reactive towards the captodative radical generated by oxazolidinone **1** (inducing partial racemization of the dynamic axial chirality) or less prone to get oxidized into a radical (both mechanisms can be proposed in our case as we observed in several experiments either dimers of compound **1** or dimers of acetophenone as byproducts).

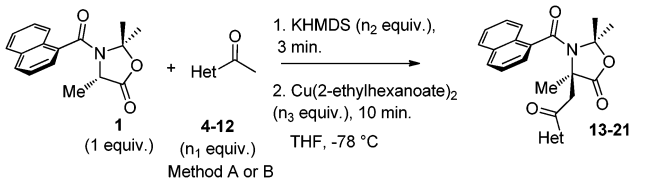
Table 3 Scope of heterocoupling with substituted acetophenones



Entry	R	Method[a]	Temp. (°C)	t (min)	Compound	Yield (%)	ee[b] (%)
1	H	A	−78	30	**3a**	45	64
2	H	A	−85	10	**3a**	44	65
3	H	A	−85	30	**3a**	48	61
4	H	B	−78	30	**3a**	37	64
5	NO_2	A	−78	10	**3b**	73	30
6[c]	NO_2	B	−78	10	**3b**	58	45
7	NO_2	A	−85	10	**3b**	77	32
8	Br	A	−85	10	**3c**	60	41
9	OMe	A	−78	10	**3d**	56	68
10	OMe	A	−85	10	**3d**	58	60
11	OMe	B	−78	10	**3d**	38	74
12	NMe_2	A	−78	30	**3e**	56	71
13	NMe_2	B	−78	10	**3e**	23	44

[a] Method A: $n_1 = 4$, $n_2 = n_3 = 6$; compounds **1** and **2** are deprotonated in the same flask; method B: $n_1 = 3$, $n_2 = 7$, $n_3 = 4$; compounds **1** and **2** are deprotonated in separated flasks: deprotonation of **2** for 10 min, then deprotonation of **1**, and gathering the two enolates for 3 min, then oxidation. [b] Determined by chiral stationary-phase HPLC. [c] $n_1 = 4$, $n_2 = 8$, $n_3 = 5$.

Table 4 Scope of heterocoupling with acetyl-heteroaromatics



Entry	Het	Method[a]	Compound	Yield (%)	ee[b] (%)
1[c]	4	B	**15**	12	60
2[c]	5	A	**16**	16	91
3[c]	5	B	**16**	0[e]	—
4[c]	6	A	**17**	46	87
5	6	B	**17**	64	82
6[d]	6	B	**17**	34	44
7	7	B	**18**	43	80
8	8	A	**19**	24	94
9	8	B	**19**	0[e]	—
10	9	A	**20**	57	88
11	9	B	**20**	82	81
12	10	B	**21**	70	50
13	11	B	**22**	21	82
14	12	B	**23**	75	45
15	13	B	**24**	43	75
16	14	B	**25**	58	72

[a] Method A: compounds **1** and **4–12** are deprotonated in the same flask, $n_1 = 3$, $n_2 = 10$ and $n_3 = 4$; method B: compounds **1** and **4–12** are deprotonated in separated flasks, $n_1 = 3$, $n_2 = 7$ and $n_3 = 4$; deprotonation of **4–12** for 10 min, then deprotonation of **1** for 3 min, and gathering the two enolates for 3 minutes, then oxidation. [b] Determined by chiral stationary-phase HPLC. [c] In these cases, $n_1 = 4$ and oxidation time was 30 min. [d] $n_1 = 1.5$, $n_2 = 5$ and $n_3 = 3$ and oxidation time was 30 min. [e] No reaction was observed under these conditions.

Considering the importance of the electron-density of the aromatic substituent, we decided to apply the oxidative coupling reaction to electron-rich heterocycles. We selected 3-acetylindoles with different *N*-protecting groups and substituents together with 2-acetylated benzofuran, pyrrole, thiophene and furan under different reaction conditions (*in situ* or separate deprotonation). The results are reported in Table 4.

The best protecting group for indole is Boc carbamate (entries 1–5). We observed that separate deprotonation improved the yield but slightly decreased a bit the enantiomeric excess (entries 4 and 5 or 10 and 11). In some cases, separate deprotonation did not lead to the expected product (entries 3 and 9) probably because of lower stability of the enolate. In almost all cases, we were pleased to obtain the expected compounds with enantiomeric excesses above 72% and in reasonable yields in many cases. The best result was obtained, using compound **9**, with compound **20** being obtained under *in situ* conditions with 88% ee and in 57% yields. This reaction was also performed on a 2 mmol scale (with 4 equiv. of indole **9**) with the same success (and 1 g of unreacted indole **9** was recovered after purification, which compensates the drawback of the coupling partner excess).

To conclude, we have developed the first enantioselective heterocoupling of enolates. We showed thus that MOC was adapted to this reaction with electron-rich ketones, the captodative character of the radical issued from **1** being probably essential to this result. 1,4-Dicarbonyl motifs with a quaternary centre were obtained in a good yield and a high enantiomeric excess up to a 2 mmol scale. Further studies on radical coupling with other types of partners are under investigation in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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