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Three-component synthesis of a library of *m*-terphenyl derivatives with embedded β-aminoester moieties

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KEYWORDS. Terphenyl derivatives; carbocycle construction; multicomponent reactions; chalcones.

ABSTRACT. The three-component reaction between alkyl- or arylamines, β-ketoesters and chalcones in refluxing ethanol containing a catalytic amount of Ce(IV) ammonium nitrate allowed the construction of a large library of highly substituted dihydro-*m*-terphenyl derivatives containing β-alkylamino- or β-arylamino ester moieties. This process generates three new bonds and one ring and proceeds in high atom economy, having two molecules of water as the only side product. Another domino process, in which the original MCR was telescoped with a subsequent aza Michael/retro-aza Michael sequence, allowed the one-pot preparation of a library of compounds with a *N*-unsubstituted β-aminoester fragment. Finally, in order to extend the structural diversity of these libraries, we also examined the aromatization of the central ring of our compounds in the presence of DDQ. This reaction sequence did not affect the integrity of a stereogenic center belonging to the amino component.

INTRODUCTION

Teraryl moieties are important structural motifs that are inherent to many natural products and synthetic molecules that have been widely used as building blocks in medicinal chemistry[1] and materials science. In particular, *m*-terphenyl (MTPs, Figure 1) constitutes the structural core of several terphenyl natural products[2] such as trifucol,[3] dictyoterphenyl[4] and the regioisomeric neosesquilignans macranthol,[5] dunnianol[6] and simonsinol.[7] Among these compounds, macranthol has shown interesting biological properties such as the ability to promote hippocampal neuronal proliferation.[8] Synthetic *m*-terphenyl derivatives have also exhibited various pharmacologically interesting properties such as antiprotozoal activity,[9] cyclooxygenase 2 inhibition[10] and antiarthritic activity.[11] Furthermore, MTPs have also attracted much attention because of their high thermal stability and unusual electronic properties due to their broken conjugation, making them particulary important in materials science. Some applications in this area include the construction of artificial helical and doubly helical polymers,[12] dye-sensitized solar cells,[13] organic light emission diodes (OLEDs),[14] liquid crystals for optoelectronic applications[15] and cation sensors.[16] Finally, terphenyl frameworks are the basis of several types of structures of relevance in supramolecular chemistry[11,14,17] and have been used as efficient ligands for metal-catalyzed synthetic reactions.[18]

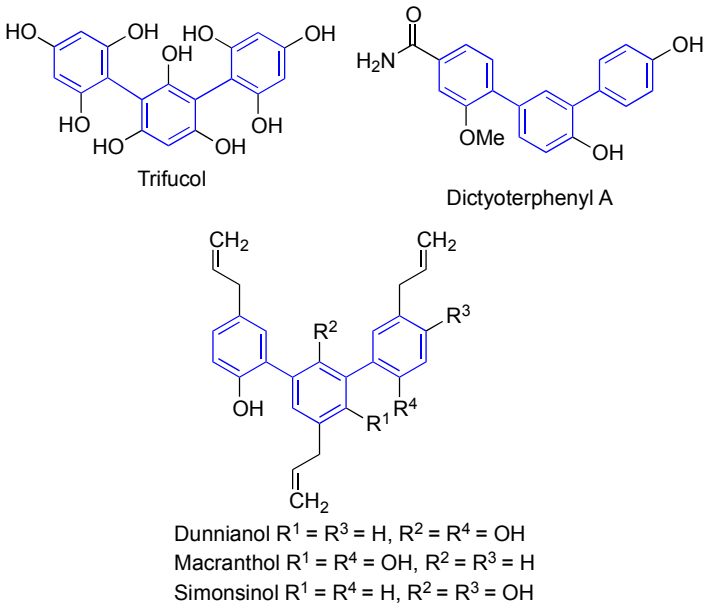
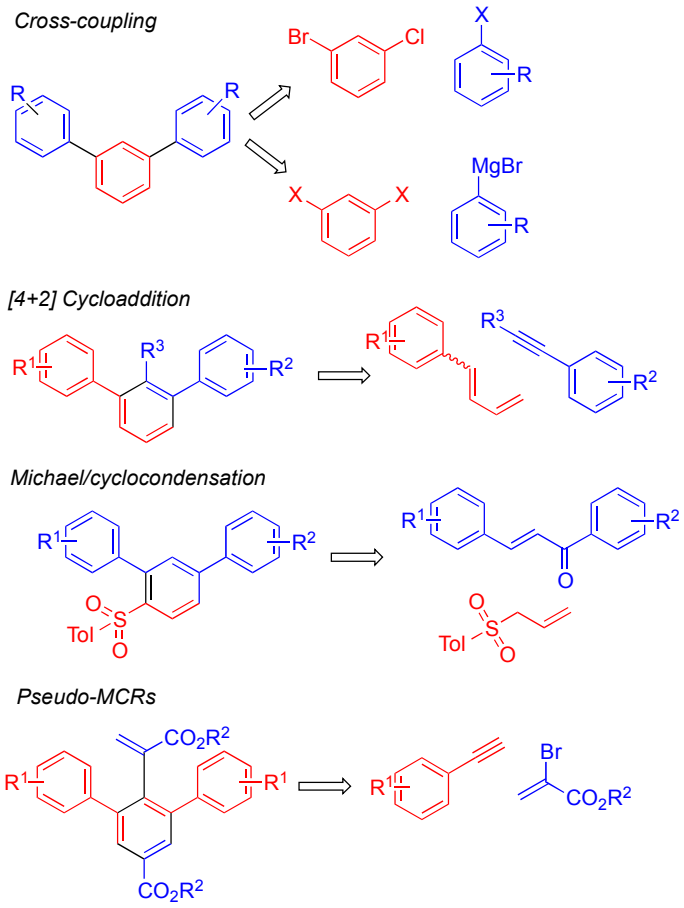


Figure 1. Structures of representative MTP-derived natural compounds

The importance of terphenyl frameworks has stimulated the development of a fair amount of synthetic methodology in this area.[19] For the case of *m*-terphenyls, the most commonly employed strategies (Scheme 1) can be summarized as follows: (a) aryl-aryl bond formation involving transition-metal-catalyzed reactions;[19] (b) reaction of 1,2,3-trihalobenzenes[20] or 2-lithio-1,3-dihalobenzenes[21] with an aryl Grignard reagent via aryne intermediates; (c) generation of the central benzene ring by cycloaddition reactions[22] or Michael-cyclocondensation sequences;[23] (d) pseudomulticomponent reactions between 2-bromoacrylates and phenylacetylenes *via* a Sonogashira-cycloaddition mechanism.[24]

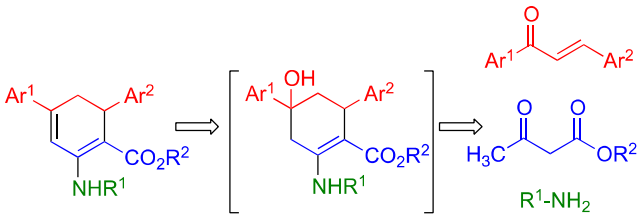


Scheme 1. Representative disconnections of the *m*-terphenyl framework

All the methods summarized above furnish fully aromatic terphenyl derivatives. However, the removal of aromaticity from bioactive compounds is a well-established methodology for improving aqueous solubility, a key objective in drug discovery and development.[25] Therefore, methodology leading directly to such systems is important in drug discovery programs. In particular, the development of multicomponent reactions leading to pharmacologically relevant frameworks having partially saturated rings is of great importance in view of the high synthetic efficiency associated to these reactions and their potential in the construction of diversity-

oriented libraries.[26] In this context, we have described in preliminary fashion a diastereoselective three-component reaction that affords 1,3-diaryl-1,2,3,4-tetrahydrobenzene derivatives from alkylamines, β-ketoesters, and chalcones in the presence of catalytic Ce(IV) ammonium nitrate (CAN).[27] Subsequently, we employed this reaction as the basis for one-pot routes to heterocyclic systems such as quinazolines[28] and carbazoles,[29] without isolation of the intermediate terphenyls. Almost simultaneously with our initial communication, Shi reported another multicomponent process from malononitrile, nitrostyrenes and arylmethylenemalononitriles leading to tetrahydro-*m*-terphenyls as diastereomer mixtures.[30] Recently, Li described a reaction essentially identical to ours that led to cyclohexa-1,3-dien-2-amines but that (with two exceptions) was restricted to aromatic amines and required the use of stoichiometric amounts of the neurotoxic and highly reactive $AlCl_3$ as a promoter.[31]

Due to the importance of the *m*-terphenyl framework, we now describe in full our work on the optimization of the multicomponent synthesis of libraries of dihydroterphenyls from acyclic precursors (Scheme 2). We also include our studies on their dehydrogenation in order to increase the scope of library generation by this method.[32] All these libraries have the further advantage that the compounds contain a β-aminoester substructure, a very attractive moiety in drug discovery projects because of its presence in a large number of pharmacologically relevant structures with varied activities.[33] Furthermore, methods for obtaining cyclic β-aminoacid or β-aminoesters are scarce in the literature[34] in spite of their considerable importance in medicinal chemistry, both for themselves and as components of β-peptides and peptidomimetics resistant to proteolysis.



Scheme 2. Multicomponent disconnection of 5,6-dihydroterphenyls examined in this article

RESULTS AND DISCUSSION

The structural diversity of the starting materials (chalcones **1**, β-dicarbonyl compunds **2** and amines **3**) employed for the construction of our library is summarized in Figure 2. The starting chalcones **1** were either commercially available or prepared from aromatic ketones and aromatic aldehydes according to literature procedures.[35] All dicarbonyl compounds **2** and amines **3** were of commercial origin.

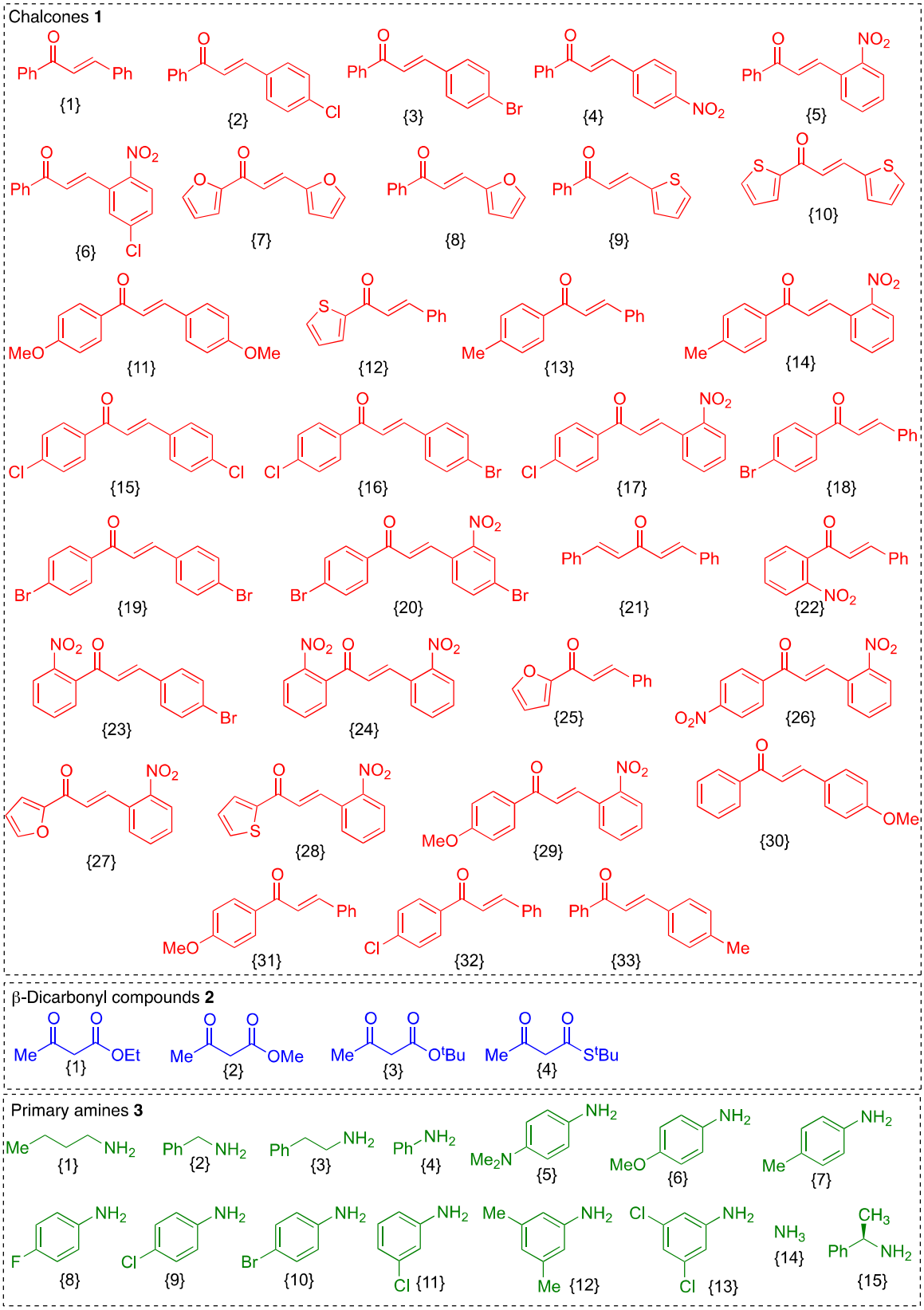


Figure 2. Structural diversity of chalcones **1,** β-dicarbonyl compounds **2** and primary amines **3**

Although our preliminary study had revealed conditions for the synthesis of 1-hydroxy-1,2,3,6-tetrahydro-*m*-terphenyl derivatives via a multicomponent reaction, the relatively low stability of these compounds made its application to the library construction somewhat impractical. This prompted us to seek the *in situ* dehydration of these intermediates to furnish dihydroterphenyls. Our optimization study was performed for the model reaction leading to compound **4**{1,1,1} from ethyl acetoacetate, butylamine and the unsubstituted chalcone. It involved initially the use of a variety of Lewis acids (ytterbium triflate, yttrium triflate, indium trichloride, CAN) at 10 mol% concentration in refluxing ethanol, with the best results being obtained for the latter catalyst (entries 1-4). Lowering the catalyst load to 5 mol% did not cause an appreciable change (entry 5), but a drop in yield was observed upon a further reduction of catalyst to 2.5% (entry 6). Some alternative solvents were also examined with no improvement over ethanol (methanol, entry 7; acetonitrile, entry 8). The use of focused microwave irradiation in EtOH in the presence of 5% CAN allowed a dramatic decrease in reaction time (1 *vs* 14 h), although the yield was slightly lower (entry 9). Finally, a control experiment showed that the reaction gave only a small amount of the product in the absence of catalyst.

Table 1. Optimization studies for the synthesis of compound **4**{1,1,1}.

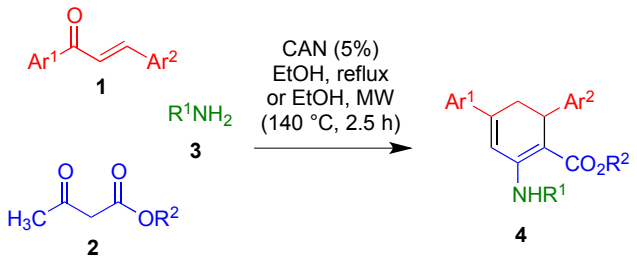
Entry	Catalyst	Conditions[a]	Solvent	Yield, %
1	$Yb(OTf)_3$, 10%	A	EtOH	58
2	$Y(OTf)_3$, 10%	A	EtOH	15

3	$InCl_3$, 10%	A	EtOH	45
4	CAN, 10%	A	EtOH	89
5	CAN, 5%	A	EtOH	88
6	CAN, 2.5%	A	EtOH	60
7	CAN, 5%	A	MeOH	80
8	CAN, 5%	A	CH_3CN	67
9	CAN, 5%	B	EtOH	75
10	None	A	EtOH	Traces

[a]Reaction conditions: A. Reflux temperature of the chosen solvent, 14 h. [b]Focused microwave, 140 °C, 1 h

With these results in hand, we proceeded to build the compound library (Scheme 3 and Table 2). We used in most cases the microwave-assisted conditions due to the shorter reaction times, in spite of the slightly lower yields. For scaling up the reactions, the reflux conditions were preferable. A comparison between both conditions has been carried out in some cases and the results can be found in Table 2 (entries 10, 11, 16, 20, 23 and 25).

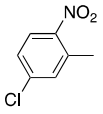
The microwave-promoted reaction was normally carried out at 140 °C for 2.5 h, except in those cases where the Ar^1 or Ar^2 groups bear an *o*-nitro substituent; these reactions required only 100 °C for the same time, probably due to an enhanced electrophilicity of the chalcone (see Table 2 below, entries 10, 16, 19, 22, 23, 24).

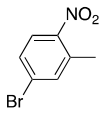


Scheme 3. Three-component synthesis of dihydro-*m*-terphenyl derivatives with an embedded β-aminoester moiety

The results obtained in the reaction with alkylamines are summarized in Table 2, and prove the possibility to introduce structural variations either at the alkylamino group (R^1 substituent) and at the ester functional group (R^2 substituent), including the preparation of thioesters (entry 2). Regarding the terphenyl framework itself, our results show that the reaction tolerates well the presence of unsubstituted phenyl groups and phenyls bearing either electron-releasing or electron-withdrawing groups both at Ar^1 (unsubstituted phenyl: entries 1-5, and 7-13; phenyl with electron-releasing groups: entries 6, and 14-16; phenyl with electron-withdrawing groups: entries 17-24 and 30) and at Ar^2 (unsubstituted phenyl: entries 1-6, 14, 20, 22, 25, 27 and 29; phenyl with electron-releasing groups: entry 15; phenyl with electron-withdrawing groups: entries 7-11, 16-19, 21, 23, 24 and 30). The method was rather insensitive to steric hindrance in either of the aromatic rings, as shown by the preparation of several examples of compounds **4** bearing bulky substituents at their *o*- positions (entries 22-24 for Ar^1 and 10, 11, 16, 19, 24, 30 for Ar^2). Furthermore, we also examined the introduction of several heteroaromatic substituents at Ar^1 (entries 25-28), Ar^2 (entries 12, 13, 26 and 28) or both (entries 26 and 28), and we also carried out a reaction with a vinylogous chalcone, which furnished the styryl derivative **4**{21,1,1} (entry 29).

Table 2. Results obtained in the three-component reaction starting from alkylamines

Entry	Compound	R^1	R^2	Ar^1	Ar^2	Method A[a]		Method B[b]	
						Yield, %	t, h	Yield, %	Temp,°C
1	**4**{1,1,1}	*n*-Bu	OEt	Ph	Ph	88	8	75	140
2	**4**{1,4,1}	*n*-Bu	*St*-Bu	Ph	Ph	75	8	--	--
3	**4**{1,1,2}	$PhCH_2$	OEt	Ph	Ph	78	8	--	--
4	**4**{1,3,2}	$PhCH_2$	O*t*-Bu	Ph	Ph	80	8	--	--
5	**4**{1,1,3}	$Ph(CH_2)_2$	OEt	Ph	Ph	79	8	--	--
6	**4**{13,1,1}	*n*-Bu	OEt	4-MeC_6H_4	Ph	--	--	65	140
7	**4**{2,1,1}	*n*-Bu	OEt	Ph	4-ClC_6H_4	--	--	67	140
8	**4**{3,1,1}	*n*-Bu	OEt	Ph	4-BrC_6H_4	--	--	80	140
9	**4**{4,1,1}	*n*-Bu	OEt	Ph	4-$O_2NC_6H_4$	--	--	72	140
10	**4**{5,1,1}	*n*-Bu	OEt	Ph	2-$O_2NC_6H_4$	78	8	74	100
11	**4**{6,1,1}	*n*-Bu	OEt	Ph		72	8	65	140
12	**4**{8,1,1}	*n*-Bu	OEt	Ph		--	--	68	140
13	**4**{9,1,1}	*n*-Bu	OEt	Ph		--	--	67	140
14	**4**{31,1,1}	*n*-Bu	OEt	4-$MeOC_6H_4$	Ph	--	--	73	140
15	**4**{11,1,1}	*n*-Bu	OEt	4-$MeOC_6H_4$	4-$MeOC_6H_4$	--	--	72	140
16	**4**{14,1,1}	*n*-Bu	OEt	4-MeC_6H_4	2-$O_2NC_6H_4$	75	8	67	100
17	**4**{15,1,1}	*n*-Bu	OEt	4-ClC_6H_4	4-ClC_6H_4	--	--	75	140
18	**4**{16,1,1}	*n*-Bu	OEt	4-ClC_6H_4	4-BrC_6H_4	--	--	78	140
19	**4**{17,1,1}	*n*-Bu	OEt	4-ClC_6H_4	2-$O_2NC_6H_4$	--	--	79	100
20	**4**{18,1,1}	*n*-Bu	OEt	4-BrC_6H_4	Ph	86	8	84	140
21	**4**{19,1,1}	*n*-Bu	OEt	4-BrC_6H_4	4-BrC_6H_4	--	--	84	140
22	**4**{22,1,1}	*n*-Bu	OEt	2-$O_2NC_6H_4$	Ph	--	--	83	100
23	**4**{23,1,1}	*n*-Bu	OEt	2-$O_2NC_6H_4$	4-BrC_6H_4	82	8	85	100

24	**4**{24,1,1}	*n*-Bu	OEt	2-$O_2NC_6H_4$	2-$O_2NC_6H_4$	--	--	62	100
25	**4**{25,1,1}	*n*-Bu	OEt		Ph	71	8	73	140
26	**4**{7,1,1}	*n*-Bu	OEt			--	--	70	140
27	**4**{12,1,1}	*n*-Bu	OEt		Ph	--	--	70	140
28	**4**{10,1,1}	*n*-Bu	OEt			--	--	68	140
29	**4**{21,1,1}	*n*-Bu	OEt	Ph-CH=CH	Ph	70	6	--	--
30	**4**{20,1,1}	*n*-Bu	OEt	4-BrC_6H_4		--	--	66	140

[a] Reflux in ethanol. [b] Irradiation with focused microwaves (140 °C, 2.5 h, except entries 10, 16, 19, 22, 23 and 24: 100 °C, 2.5 h), in ethanol.

Regarding the role of Ce(IV) ammonium nitrate, radical intermediates could be in principle expected due to its strong oxidant properties. However, our reaction proceeded with no appreciable loss in yield when performed in the presence of 1,1-diphenylethylene, which is a well-known radical trap. This evidence led us to conclude that in our system Ce(IV) acts simply as a Lewis acid catalyst, as in many other cases described in the literature.[36]

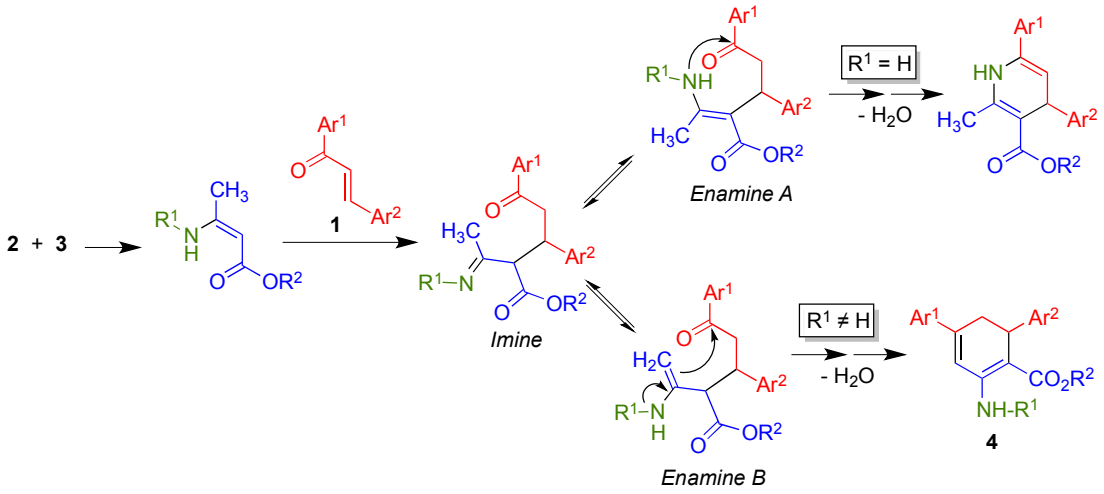
At a second stage of our study, we investigated the use of aromatic amines as the third component. As shown in Table 3, the reaction allowed the preparation of compounds bearing an unsubstituted *N*-phenyl substituent (R^1 = Ph, entries 1, 9-11, 15-18, 20 and 21), as well as compounds bearing electron-withdrawing (entries 3-6, 8 and 14) or electron-releasing (entries 2, 7, 12, 13, 19 and 22) groups at the nitrogen aromatic ring, with variations in the Ar^1 and Ar^2 aromatic rings similar to the ones described above. Compared with the previous case of

alkylamines, the reactions were slower and required a higher catalyst load (25%). These transformations were carried under reflux in all cases because the reaction times in microwave-assisted conditions were too long to be of practical value.

Table 3. Results obtained in the three-component reaction starting from arylamines

Entry	Compound	Ar^1	Ar^2	R^1	R^2	Method A	
						Yield, %	t, h
1	**4**{1,1,4}	Ph	Ph	Ph	Et	83	72
2	**4**{1,1,5}	Ph	Ph	4-$Me_2NC_6H_4$	Et	90	72
3	**4**{1,1,8}	Ph	Ph	4-FC_6H_4	Et	77	72
4	**4**{1,1,9}	Ph	Ph	4-ClC_6H_4	Et	75	72
5	**4**{1,1,10}	Ph	Ph	4-BrC_6H_4	Et	72	72
6	**4**{1,1,11}	Ph	Ph	3-ClC_6H_4	Et	58	72
7	**4**{1,1,12}	Ph	Ph	3,5-$Me_2C_6H_3$	Et	90	72
8	**4**{1,1,13}	Ph	Ph	3,5-$Cl_2C_6H_3$	Et	54	72
9	**4**{1,2,4}	Ph	Ph	Ph	Me	72	72
10	**4**{4,1,4}	Ph	4-$O_2NC_6H_4$	Ph	Et	82	72
11	**4**{5,1,4}	Ph	2-$O_2NC_6H_4$	Ph	Et	83	14
12	**4**{5,1,5}	Ph	2-$O_2NC_6H_4$	4-$Me_2NC_6H_4$	Et	87	14
13	**4**{5,1,6}	Ph	2-$O_2NC_6H_4$	4-$MeOC_6H_4$	Et	84	14
14	**4**{5,1,8}	Ph	2-$O_2NC_6H_4$	4-FC_6H_4	Et	79	14
15	**4**{29,1,4}	4-$MeOC_6H_4$	2-$O_2NC_6H_4$	Ph	Et	72	14
16	**4**{14,1,4}	4-MeC_6H_4	2-$O_2NC_6H_4$	Ph	Et	79	14
17	**4**{26,1,4}	4-$O_2NC_6H_4$	2-$O_2NC_6H_4$	Ph	Et	82	72
18	**4**{24,1,4}	2-$O_2NC_6H_4$	2-$O_2NC_6H_4$	Ph	Et	67	14
19	**4**{27,1,6}		2-$O_2NC_6H_4$	4-$MeOC_6H_4$	Et	82	14
20	**4**{7,1,4}			Ph	Et	81	72
21	**4**{12,1,4}		Ph	Ph	Et	85	72
22	**4**{28,1,6}		2-$O_2NC_6H_4$	4-$MeOC_6H_4$	Et	86	14

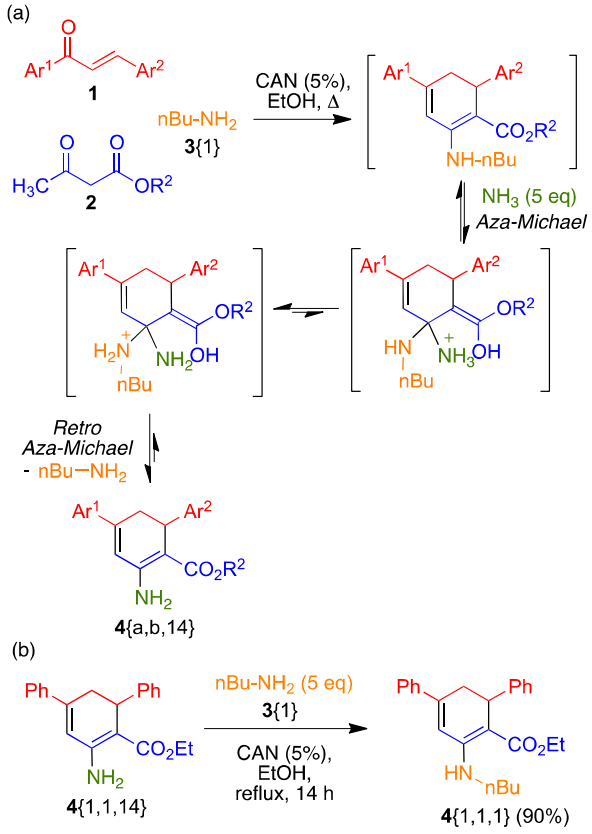
We next examined the preparation of *N*-unsubstituted derivatives, which in principle would seem to be feasible by using ammonia as the amine component. However, we have shown this reaction to afford 4,6-diaryl-1,4-dihydropyridines, which have been exploited for their neuroprotective activity.[37] This difference in behavior can be explained by the mechanistic proposal shown in Scheme 4, where the β-enaminone generated initially from **2** and **3** adds to the chalcone to furnish an imine that can tautomerize to two different enamines **A** and **B**. The first of them, more stable, can cyclize to give a dihydropyridine only if R^1 = H for steric reasons. For all other cases $R^1 \neq$ H), the only possibility is the cyclization of enamine **B** to yield compounds **4**.



Scheme 4. Proposed explanation for the difference in product selectivity between primary amines and ammonia

Due to the impossibility of employing ammonia as a starting material for our multicomponent reaction, we resorted to an indirect method for the preparation of the *N*-unsubstituted compounds. Thus, we carried out the usual three-component reaction with butylamine and, without isolation, treated *in situ* the initially formed product with ammonium formate as a source of ammonia. Presumably, under these conditions an aza-Michael/retro aza-Michael process takes

place that leads to the exchange of the butylamino and amino substituents (Scheme 5a). This exchange is reversible, as shown by the fact that the reaction between the *N*-unsubstituted compound **4**{1,1,14} and butylamine under our reaction conditions gives the *N*-butyl derivative **4**{1,1,1} in 90% yield, as shown by a separate experiment. Therefore, the aza-Michael / retro aza-Michael pathway is reversible, and the good results that we have obtained in the butylamino-amino exchange must be ascribed to equilibrium displacement because of the large excess of ammonium formate that we employ (Scheme 5b).



Scheme 5. *In situ* butylamino-amino exchange for the synthesis of *N*-unsubstituted compounds **4**

This domino process was applied to generate a library of *N*-unsubstituted compounds **4**{a,b,14} in good to excellent yields, as summarized in Table 4. As in previous cases, the versatility of the

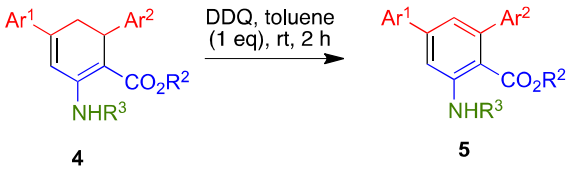
method to yield compounds **4** with variously substituted phenyl rings at Ar^1 and Ar^2, as well as heteroaryl substituents, was demonstrated.

Table 4. Results obtained in the synthesis of *N*-unsubstituted compounds **4** by a three-component reaction telescoped with an *in situ* butylamino-amino exchange

Entry	Compound	Ar^1	Ar^2	Yield, %
1	**4**{1,1,14}	Ph	Ph	96
2	**4**{30,1,14}	Ph	4-$MeOC_6H_4$	93
3	**4**{33,1,14}	Ph	4-MeC_6H_4	78
4	**4**{2,1,14}	Ph	4-ClC_6H_4	70
5	**4**{5,1,14}	Ph	2-$O_2NC_6H_4$	77
6	**4**{8,1,14}	Ph		78
7	**4**{9,1,14}	Ph		79
8	**4**{31,1,14}	4-$MeOC_6H_4$	Ph	87
9	**4**{11,1,14}	4-$MeOC_6H_4$	4-$MeOC_6H_4$	92
10	**4**{13,1,14}	4-MeC_6H_4	Ph	73
11	**4**{32,1,14}	4-ClC_6H_4	Ph	82
12	**4**{15,1,14}	4-ClC_6H_4	4-ClC_6H_4	90
13	**4**{16,1,14}	4-ClC_6H_4	4-BrC_6H_4	87
14	**4**{18,1,14}	4-BrC_6H_4	Ph	90
15	**4**{19,1,14}	4-BrC_6H_4	4-BrC_6H_4	92
16	**4**{25,1,14}		Ph	74
17	**4**{7,1,14}			77
18	**4**{12,1,14}		Ph	76
19	**4**{10,1,14}			78

Finally, in order to extend the structural diversity of our libraries, we examined the aromatization of the central ring of *m*-terphenyl derivatives **4**. Our initial attempts to perform this dehydrogenation with Pd-C at varying concentrations in several solvents at reflux conditions, gave poor results. However, as shown in Scheme 6, this transformation was easily achieved by

treatment with DDQ in toluene, at room temperature, and proceeded in excellent yields in all cases studied, leading to a general method for the synthesis of fully aromatic compounds **5** (Table 5). For the case of the *N*-unsubstituted derivatives **5**{x,1,14}, it is interesting to note that our method compares favorably with a recently described protocol involving an oxidative N-debenzylation step and that requires the use of three equivalents of DDQ.[33] In this context, it is relevant to note that oxidizing compounds are a well-known source of toxic waste, and redox economy has been identified as particularly relevant in terms of synthetic sustainability.[38]

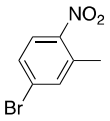
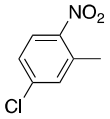


4 **5**

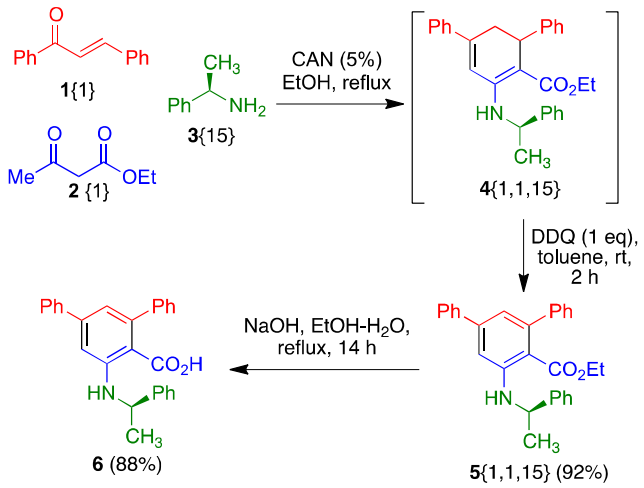
Scheme 6. Aromatization of compounds **4**

Table 5. Results obtained in the synthesis of aromatic compounds **5** by dehydrogenation of **4**

Entry	Compound	Ar^1	Ar^2	R^1	R^2	Yield, %
1	**5**{1,1,14}	Ph	Ph	H	OEt	99
2	**5**{13,1,14}	4-MeC_6H_4	Ph	H	OEt	96
3	**5**{32,1,14}	4-ClC_6H_4	Ph	H	OEt	95
4	**5**{15,1,14}	4-ClC_6H_4	4-ClC_6H_4	H	OEt	97
5	**5**{30,1,14}	Ph	4-$MeOC_6H_4$	H	OEt	97
6	**5**{19,1,14}	4-BrC_6H_4	4-BrC_6H_4	H	OEt	96
7	**5**{1,1,1}	Ph	Ph	*n*-Bu	OEt	93
8	**5**{32,1,1}	4-ClC_6H_4	Ph	*n*-Bu	OEt	92
9	**5**{10,1,1}			*n*-Bu	OEt	95

10	**5**{5,1,1}	Ph	2-$O_2NC_6H_4$	*n*-Bu	OEt	91
11	**5**{24,1,1}	2-$NO_2C_6H_4$	2-$O_2NC_6H_4$	*n*-Bu	OEt	88
12	**5**{20,1,1}	4-BrC_6H_4		*n*-Bu	OEt	92
13	**5**{6,1,1}	Ph		*n*-Bu	OEt	89
14	**5**{23,1,1}	2-$NO_2C_6H_4$	4-BrC_6H_4	*n*-Bu	OEt	94
15	**5**{19,1,1}	4-BrC_6H_4	4-BrC_6H_4	*n*-Bu	OEt	92
16	**5**{22,1,1}	2-$NO_2C_6H_4$	Ph	*n*-Bu	OEt	82
17	**5**{14,1,1}	4-MeC_6H_4	2-$O_2NC_6H_4$	*n*-Bu	OEt	90
18	**5**{21,1,1}	PhCH=CH	Ph	*n*-Bu	OEt	93
19	**5**{1,1,2}	Ph	Ph	$PhCH_2$	OEt	78[a]
20	**5**{1,3,2}	Ph	Ph	$PhCH_2$	O^t-Bu	78
21	**5**{1,1,4}	Ph	Ph	Ph	OEt	94
22	**5**{1,1,12}	Ph	Ph	3,5-$Me_2C_6H_3$	OEt	93
23	**5**{1,1,8}	Ph	Ph	4-FC_6H_4	OEt	90
24	**5**{1,1,11}	Ph	Ph	3-ClC_6H_4	OEt	92
25	**5**{1,1,9}	Ph	Ph	4-ClC_6H_4	OEt	94
26	**5**{1,1,10}	Ph	Ph	4-BrC_6H_4	OEt	96
27	**5**{1,1,13}	Ph	Ph	3,5-$Cl_2C_6H_3$	OEt	95
28	**5**{4,1,4}	Ph	4-$O_2NC_6H_4$	Ph	OEt	93
29	**5**{12,1,4}		Ph	Ph	OEt	97
30	**5**{7,1,4}			Ph	OEt	95
31	**5**{1,1,5}	Ph	Ph	4-$Me_2NC_6H_4$	OEt	94
32	**5**{1,3,14}	Ph	Ph	H	O^{t}Bu	96

As a final check of the generality of our method, we studied the reaction starting from a chiral substrate in order to investigate the possibility of racemization. As shown in Scheme 7, the multicomponent reaction involving *(E)*-1,3-diphenylpropenone **1**{1}, ethyl acetoacetate **2**{1} and (*R*)-1-phenylethan-1-amine **3**{15} afforded the corresponding dihydroterphenyl **4**{1,1,15}. This compound was isolated as a *ca*. 1:1 mixture of diastereomers, showing that the remote stereocenter at the amine side chain had no influence on the stereochemical course of the reaction. Compound **4**{1,1,15}, without purification, was aromatized under our usual DDQ conditions to give **5{1,1,15}**, which proved refractary to analysis by chiral HPLC owing to its very poor solubility in the usual reverse-phase mobile phases. To surmount this obstacle, we hydrolyzed **5**{1,1,15} under basic conditions and obtained the corresponding carboxylic acid **6**, which was more adequate for HPLC studies. Compound **6** was analyzed by HPLC with a column containing ovoalbumin as chiral stationery phase, using as reference the corresponding racemic material, which was obtained from racemic **3**{15} using the same reaction sequence. In this experiment, **6** was found to be enantiomerically pure within the detection limits of the HPLC technique.



Scheme 7. Absence of racemization in a sequence of reactions starting from a chiral amine

CONCLUSIONS

The three-component reaction between alkyl- or arylamines, β-ketoesters, and chalcones in the presence of a catalytic amount of Ce(IV) ammonium nitrate in refluxing ethanol allowed the construction of a large library of dihydro-*m*-terphenyl derivatives functionalized with β-alkylamino- or β-arylamino ester moieties by creation of the central carbocyclic ring of the terphenyl system *via* the generation of two new C-C bonds, plus an additional exocyclic C-N bond corresponding to the amino side chain. Furthermore, the overall process proceeded in high atom economy, since its only side product was water (two molecules per molecule of product). The preparation of *N*-unsubstituted derivatives was not possible by the original method, since the reaction starting from ammonia, β-ketoesters, and chalcones deviated towards the generation of 4,6-diaryl-1,4-dihydropyridines. This problem was solved by designing a more complex one-pot domino process, in which the original MCR was telescoped *in situ* with a subsequent aza

Michael / retro aza-Michael sequence. The aromatization of the central ring of the dihydro-*m*-terphenyl derivatives was readily achieved in the presence of DDQ at room temperature. This reaction sequence did not alter the integrity of a stereogenic center at the nitrogen side chain.

EXPERIMENTAL SECTION

General procedure for the preparation of chalcones 1 represented by the synthesis of 1{1}. This compound was synthesized according to a reported procedure.[39] A solution of acetophenone (3.15 mL, 27 mmol) and benzaldehyde (2.7 mL, 27 mmol) in ethanol (120 mL) was added 1.1 mL of 6M aqueous sodium hydroxide solution. The reaction was stirred at room temperature and monitored by TLC for completion. The precipitated solid was collected by filtration, washed with water and hexane and purified by recrystallization from ethanol, affording chalcone **{1}.** The desired product was obtained as white solid (3.9 g, 70% yield) and used for next step without further purification.

General procedure for the preparation of *N*-alkyl substituted dihydro-*m*-terphenyls 4{a,b,1-3}, represented by the synthesis of 4{1,1,1}.

Method A

To a stirred solution of the ethyl acetoacetate (0.55 mL, 4.36 mmol) and butylamine (0.56 mL, 5.67 mmol) in ethanol (25 mL) was added CAN (120 mg, 0.21 mol). Stirring was continued for 30 min at room temperature. *(E)*-1,3-Diphenylpropenone (1.0 g, 4.80 mmol), (1.1 eq) was then added to the stirred solution and the mixture was heated under reflux for 8 hours. After completion of the reaction, as indicated by TLC, the mixture was dissolved in ethyl acetate (50 mL), washed with water, brine, dried (anhydrous Na_2SO_4), and the solvent was evaporated under reduced pressure. Final products were purified by flash silica column chromatography eluting

with a petroleum ether-ethyl acetate mixture (9/1, v/v) and obtained as yellow solid (1.44 g, 88% yield).

Method B

To a microwave tube containing a solution in EtOH (2 mL) of *(E)*-1,3-diphenylpropenone (1.0 g, 4.80 mmol) and CAN (120 mg, 0.21 mol) was added ethyl acetoacetate (0.55 mL, 4.36 mmol) and butylamine (0.56 mL, 5.67 mmol). The tube was sealed, placed in the cavity of a CEM Discover microwave oven and subjected to microwave irradiation at 140 ºC and 200 W. After a period of 2-3 min, the temperature remained constant at 140 ºC. The reaction was performed at 100 ºC during 2.5 hours for the preparation of some compounds, namely **4**{5,1,1}, **4**{14,1,1}, **4**{17,1,1}, **4**{22,1,1}, **4**{23,1,1} and **4**{24,1,1}. After completion of the reaction (2.5 hours), the tube was cooled to room temperature and the solvent was removed in vacuum to dryness and purified by column chromatography on silica gel eluting with petrol ether/EtOAc (9/1, v/v) and obtained as yellow solid (1.23 g, 75% yield).

General procedure for the preparation of *N*-aryl substituted dihydro-*m*-terphenyls {a,b,4-13} represented by the synthesis of 4{1,1,4}.

A solution of aniline (0.61 mL, 6.72 mmol), ethyl acetoacetate (0.79 mL, 6.24 mmol), (*E*)-1,3-diphenylpropenone (1.0 g, 4.80 mmol) and CAN (263mg, 0.48 mmol) in EtOH (20 mL) was refluxed for 72 h. After completion of the reaction, the reaction mixture was cooled, diluted with ethyl acetate and washed with 1 M hydrochloric acid (2 x 5 mL), saturated sodium bicarbonate solution (2 x 5 mL) and brine (5 mL). The organic phase was dried and the solvent was evaporated under reduced pressure and the oily residue was purified by column chromatography on silica gel, eluting with petroleum ether/EtOAc (8/2, v/v) and the target compound was obtained as a yellow solid (1.6 g, 83% yield)

General procedure for the preparation of *N*-unsubstituted dihydro-*m*-terphenyls {a,b,14} represented by the synthesis of 4{1,1,14}.

To a microwave tube containing a solution in EtOH (2 mL) of *(E)*-1,3-diphenylpropenone (417 mg, 2.00 mmol) and CAN (55 mg, 0.1 mmol) was added ethyl acetoacetate (0.23 mL, 1.82 mmol) and butylamine (0.23 mL, 2.37 mmol). The tube was sealed, placed in a CEM Discover microwave oven and subjected to microwave irradiation, programmed at 150 ºC and 200 W. After a period of 2-3 min, the temperature remained constant at 150 ºC. After 2.5 hours, the tube was cooled to room temperature, ammonium formate (5 eq) was added to the mixture and the reaction was continued under the same conditions for additional 60 minutes. The tube was cooled to room temperature and the solvent was removed to dryness *in vacuo*. The residue was purified by column chromatography on silica gel eluting with petrol ether/EtOAc (1/1, v/v) and the target compound was obtained as a yellow solid (613 mg, 96% yield).

General procedure for the aromatization of dihydro derivatives represented by the synthesis of 5{1,1,1}.

To a stirred solution of ethyl-6-butylamino-2,4-diphenyl-2,3-dihydro benzoate (563 mg, 1.5 mmol) in toluene (10 mL) was added DDQ (408 mg, 1.8 mmol) and the reaction mixture was stirring at room temperature for 2 h. After extraction with ethyl ether (50 mL x 3), the combined extracts were washed with H_2O (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*, to give a residue that was purified by flash chromatography on silica gel with petroleum ether-ethyl acetate mixture (9:1) and obtained as yellow solid (521 mg, 93% yield).

Synthesis of (*R*)-5'-(1-phenylethylamino)-[1,1':3',1''-terphenyl]-4'-carboxylic acid (6). To a stirred solution of ethyl 5'-((1-phenylethyl)amino)-[1,1':3',1''-terphenyl]-4'-carboxylate **5**{1,1,15}

(745 mg, 177 mmol) in EtOH (30 mL), was added 6M NaOH (20 mL) and the reaction mixture was heated under reflux overnight. Afterwards, the mixture was cooled down to room temperature and the NaOH was neutralized with HCl to pH 1. The aqueous phase was extracted with dichloromethane (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield the product as a pale brown solid (610 mg, 88%).

HPLC study of compound 6. The enantiomeric purity of compound **6** was studied with an ULTRON ES-OVM analytical column, 150 mm in length and 4.6 mm internal diameter and particle size 5 μm. A 7:3 mixture of NaH_2PO_4 aqueous buffer (pH 5.7) and iPrOH was employed as eluent. Flow rate was 1 ml/min and detection was performed by UV (358 nm), and each experiment was run for 20 min. The retention times were of the 7.21 min 8.56 min for the *S* and *R* enantiomers, respectively.

ASSOCIATED CONTENT

Supporting Information. The following file is available free of charge: Characterization data and copies of spectra of compounds **4 - 6** (PDF).

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ABBREVIATIONS

CAN, cerium(IV) ammonium nitrate; DDQ, dichlorodicyanoquinone.

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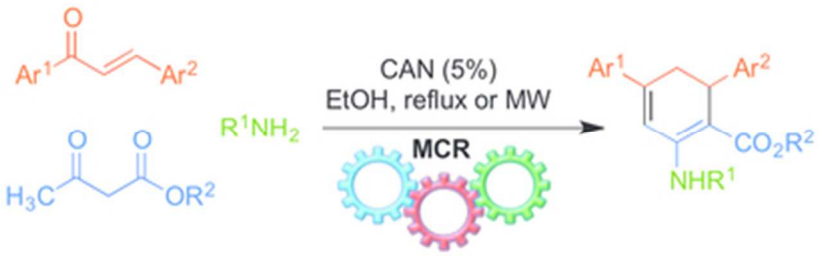

Graphical Abstract

34x10mm (300 x 300 DPI)