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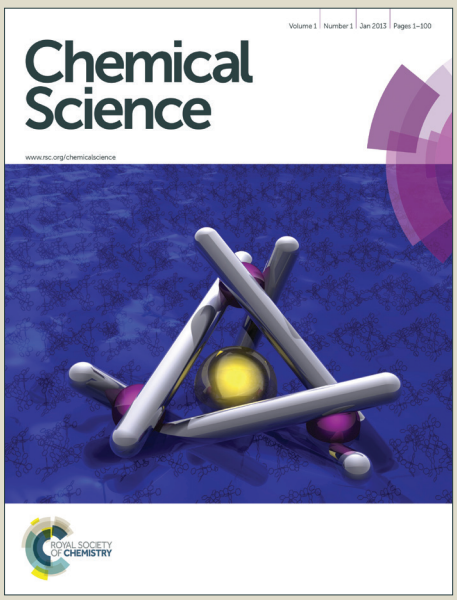

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Transition metal free Asymmetric and Diastereoselective Allylic Alkylation using Grignard reagents: Construction of vicinal stereogenic centers via Kinetic resolution.

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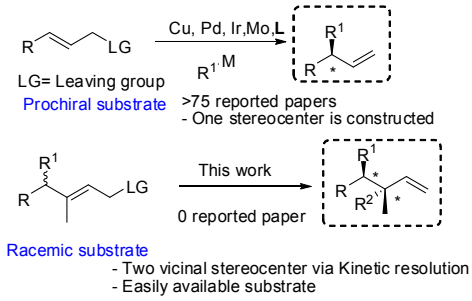
The first transition metal free diastereoselective and enantioselective AAA has been disclosed leading to the construction of vicinal tertiary/quaternary centers via a kinetic resolution protocol starting from readily available starting material. This procedure is chemically appealing since no consecutive AAA or stereoselective metal catalyzed/ chiral ligand AAA are required to construct the two stereocenters.

The asymmetric construction of sterically encumbered vicinal stereogenic centers is vital for synthetic chemists due to the abundance of such patterns in bioactive and natural compounds. The formation of quaternary centers in the context of AAA (Asymmetric Allylic Alkylation) [1] remains a great challenge because the construction of such centers is complicated by nonbonded interaction between the different carbons [2]. The issue is even more exacerbated by the presence of a vicinal stereocenter on the substrate or on the nucleophile. The steric demand is increased and the use of the appropriate catalyst to induce both diastereoselectivity and enantioselectivity remains a current challenge to tackle (Scheme 1).



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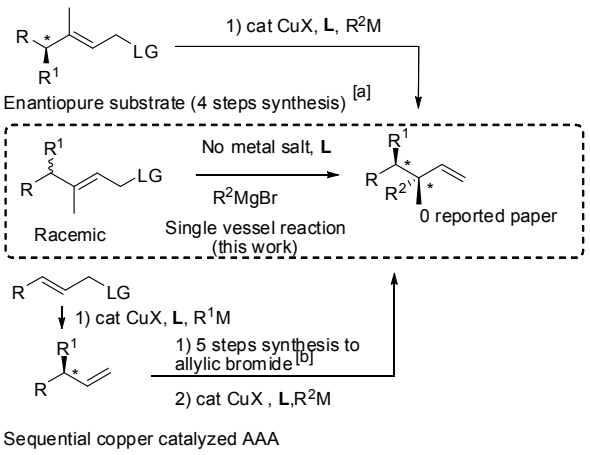
†Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

Scheme 1: Challenge in metal catalyzed AAA: Single vessel reaction to generate vicinal stereocenters. M= Mg, Zn, Al, B. L= Chiral ligand.

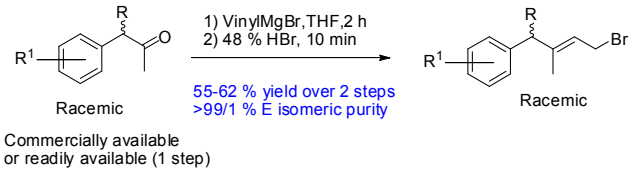
These congested stereochemical structures could be also synthesized using various transition metal catalyzed methods, such as Ir and Mo catalyzed AAA (soft nucleophile) [3,4,5], Pd-catalyzed enolate addition cascade,[6] Cu catalyzed asymmetric Claisen rearrangements [7], Pd catalyzed trimethylenemethane cycloadditions [8] or allylic alkylation of aldehyde with stereodivergent dual catalysis [9]. During these last years, we and others have devoted strong efforts to develop highly efficient transition metal free AAA using Grignard reagents, catalyzed by a bidendate N-Heterocyclic Carbene (NHC) ligand [10]. The aim was to build quaternary centers in a wide array of structurally different substrates that cannot be obtained using conventional metal catalyzed methodology [11]. Therefore we have already reported the construction of quaternary fluoroalkyl centers [12] followed by the first catalytic formation of cyclic quaternary centers with high enantioselectivity values [13]. In contrast to prochiral substrates, the use of a substrate bearing a racemic tertiary centers in alpha position of the reactive centers on the allylic bromide remains undisclosed in the literature. Using such a substrate the steric hindrance as well as the control of the diastereoselectivity without a transition metal emerged as the main challenges. Herein we report our recent success in the elaboration of a diastereoselective and enantioselective transition metal free AAA leading to the formation of a vicinal tertiary/quaternary centers catalyzed by a bidendate NHC ligand via a kinetic resolution process [14]. The following criteria have been proposed by Jacobsen as necessary conditions for a practical kinetic resolution, and this methodology respects the Jacobsen's criteria [15]. The racemic starting compound is easily available and inexpensive (2 steps). The resolution proceeds selectively at low catalyst loadings (2 mol % here), and the separation of starting material and product is facile (0.5 R_f difference in silica gel chromatography). This procedure is chemically appealing since no consecutive metal catalyzed AAA is needed to construct the requisite two tertiary stereocenters or the use of enantiomerically pure starting material (derived from chiral pool) to perform a metal catalyzed stereoselective AAA mediated by a chiral

ligand (Scheme 2). Crucially both strategies led to the construction of less challenging two vicinal tertiary stereocenter [16].

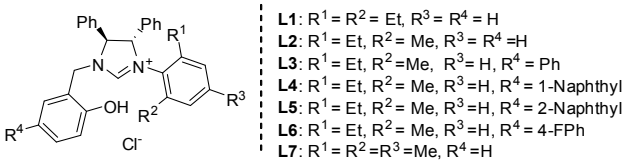


Scheme 2: Single vessel reaction versus sequential copper catalyzed AAA and copper/chiral ligand catalyzed AAA starting from enantiopure substrate. L= Chiral ligand. M= Metal (usually Zn, Al or Mg). [a] Starting from (R)-Phenylpropionic acid. [b] Oxidative cleavage, addition of Methyl Grignard followed by oxidation to ketone, Vinyl Grignard and 48 % HBr.

In our case the substrate could be easily available from the appropriate ketone (1 step from commercially available source) in a two steps procedure (addition of vinyl Grignard to the ketone followed by treatment with 48 % HBr).

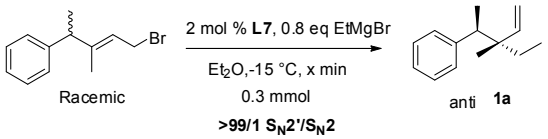


Scheme 3: General synthesis of the substrates.



Scheme 4: Chiral ligand used.

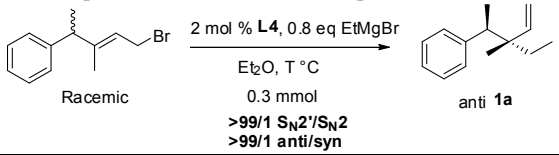
We began our investigation by selecting **1a** as target product. First, we needed to probe the possibility of a Kinetic Resolution. The quench of various aliquots after different reaction times gave informations of the correlation between the enantioselectivity and the conversion at a certain temperature using ligand **L7** (Table 1).



Entry	Time [c]	Conversion % [a]	anti/syn [a]	e:r % [b]
1	10 min	42	100/0	85:15
2	15 min	50	100/0	82:18
3	20 min	59	100/0	75:25
4	60 min	77 [c]	100/0	68:32
5	120 min	100 [c]	100/0	50:50

Table 1: [a] Ratio determined by ^{1}H-(NMR). [b] Determined using chiral GC. [c] 1.6 eq of Grignard employed.

The first striking observation is the formation of only the anti diastereoisomer (substrate control). Interestingly the anti diastereoselectivity has been also observed by Nakamura on the same substrate when using stoichiometric amount of copper with organozinc reagent, albeit with low gamma-regioselectivity and in racemic fashion [17]. After 2 h of reaction the reaction reached full conversion and 0 % ee was measured (Table 1. Entry 5). Reducing the reaction time to 60 min 77 % conversion was reached with an enantiomeric excess of 35 % ee (Table 1. Entry 4). After 20 min we could reach 59 % conversion with an increase enantiomeric excess of 50 % ee (Table 1. Entry 3). Finally by fine tuning of reaction time a quench after 15 min afforded 50 % conversion with the best hit concerning the enantioselectivity with a value of 64 % ee (Table 1. Entry 2).
With this result in hand we decided to perform a screen of ligands at -15°C on a reaction time of 15 min to try to improve the enantioselectivity. Among all the tested ligands (Scheme 4) **L4** turned out to be the best ligand (See supporting information for details). Next, to optimize the enantioselectivity, the reaction was performed at different temperatures (Table 2).

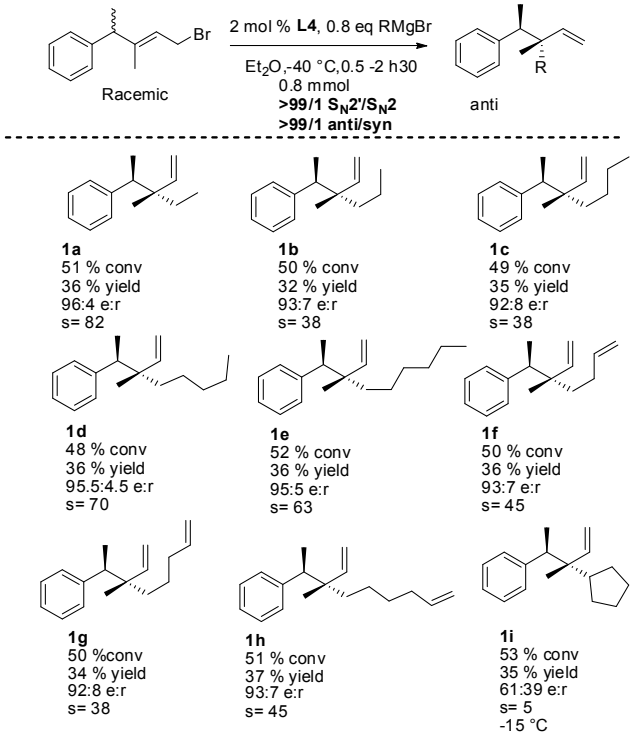


Entry	Time [f]	T (°C)	Conversion % [a]	e:r % [b]
1	15 min	-15 °C	50 (35) [c]	91:9
2	25 min	-30 °C	50	92.5:7.5
3	45 min	-40 °C	52 (34) [c]	96:4 (S,S) [e]
4	120 min	-50 °C	5	- [d]

Table 2: [a] Ratio determined by ^{1}H-(NMR). [b] Determined using chiral GC. [c] Isolated yield after silica gel column chromatography on 0.8 mmol scale. [d] Not determined. [e] Absolute configuration: see supporting information for details. [f] Time to reach 50 % conversion.

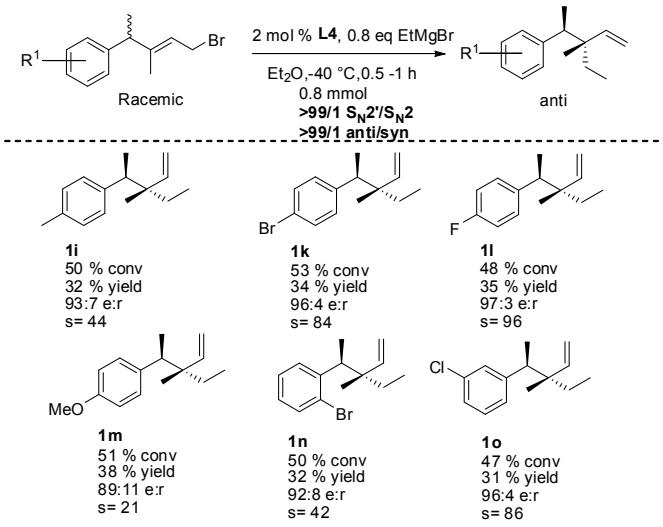
By lowering the temperature to -40 °C we could improve the enantioselectivity to 92 % ee with no erosion of the isolated yield using our best ligand **L4** (Table 2. Entry 3). By further lowering to -50°C a complete inhibition of the reaction occurred (Table 2. Entry 4). Therefore, the best conditions are 2 mol % of **L4** at -40 °C in diethyl ether. Noteworthy, the use of catalytic amount of 2 mol % CuTc (Copper thiophene carboxylate) and **L4** led to a non synthetically useful equimolar mixture of S_N2 and S_N2' products.

With the best conditions in hand the scope of Grignard reagents was further explored (Scheme 5). The introduction of several primary Grignard reagents could be performed **1a-1h** with good isolated yield, very good enantioselectivity values and, crucially, with perfect diastereoselectivity and regioselectivity. The reaction is tolerant with the respect to the chain length of the primary Grignard reagent employed. Noteworthy, the introduction of secondary bulky Grignard reagent in **1i** worked with equal level of regioselectivity, diastereoselectivity and isolated yield albeit with lower enantiomeric value. The selectivity factor has been calculated using equations reported by Kagan [18].



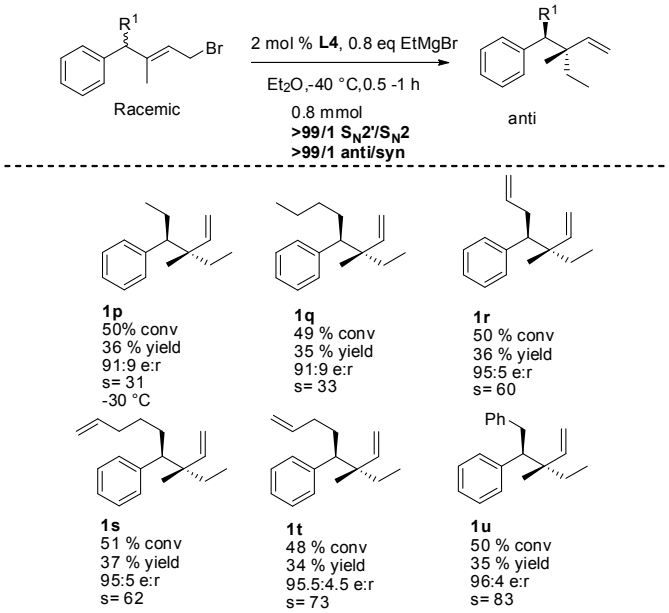
Scheme 5: Scope of nucleophiles. Isolated yield after column chromatography using silica gel on 0.8 mmol scale. Ratio determined by ^{1}H-(NMR). Determined using chiral GC. s= selectivity factor.

The substitution pattern on the aromatic ring was then explored on **1j-1o** (Scheme 6). The reaction is tolerant to both moderately electron donating or electron withdrawing groups on the aromatic part of the substrate, in para position, affording the desired adducts **1j-1l** with excellent results with respect to the regioselectivity, diastereoselectivity, enantioselectivity and chemical yield. The only limitation is the lower enantioselectivity value obtained when a highly donating electron methoxy group is present on the product **1m**. The aromatic ring could be equally substituted in ortho or meta position with no notable influence on the outcome of the reaction **1n-o** (Scheme 6).



Scheme 6: Substituted aromatic allylic bromide. Isolated yield after column chromatography using silica gel on 0.8 mmol scale. Ratio determined by ^{1}H-(NMR). Determined using chiral GC. s= selectivity factor.

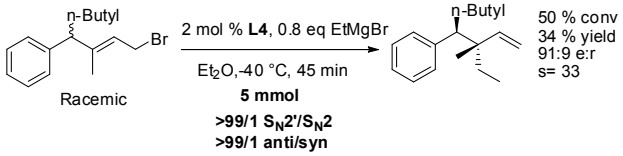
After having delineated the tolerance of the reaction concerning the Grignard reagent and substitution pattern on the aromatic group, several new substrates were investigated (Scheme 7). The use of different alkyl groups in the benzylic position of the substrate afforded the desired adducts **1p-1u** in excellent results. As a general trend the increase of the length of the aliphatic chain or the use of sterically encumbered group such as benzyl moiety provided good to excellent enantioselectivity values (Scheme 7).



Scheme 7: Substituted allylic bromide on benzylic position. Isolated yield after column chromatography using silica gel on 0.8 mmol

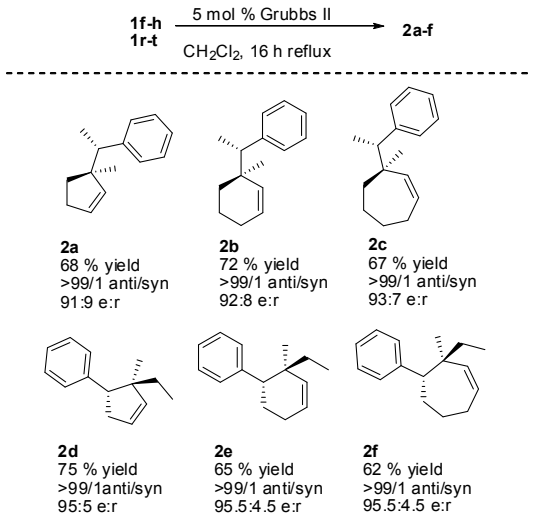
scale. Ratio determined by ^{1}H-(NMR). Determined using chiral GC or chiral SFC. s= selectivity factor.

To prove the robustness of the methodology, the reaction was run on a larger scale (5 mmol) with no erosion of the enantioselectivty or regioselectivity (Scheme 8).



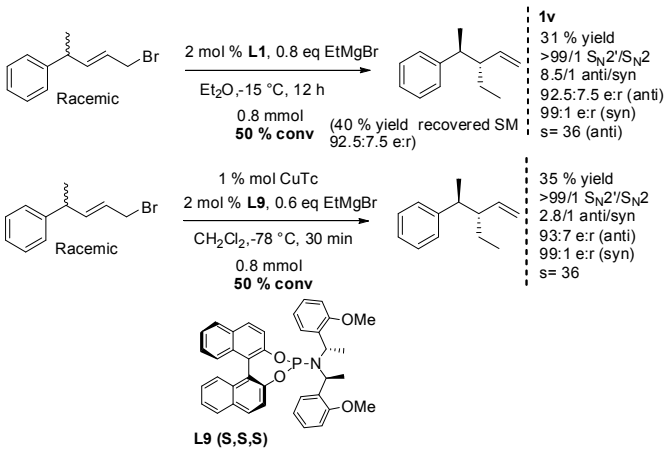
Scheme 8: Scale-up experiment.

All the resulting products can be further elaborated into more complex structures. As application we propose to use the terminal double bond of the Grignard reagents with various carbon linkers or the double bond present on the group situated on the benzylic position of the starting material in a ring closing metathesis (Scheme 9). By using 5 mol % Grubbs second generation catalyst in refluxing dichloromethane, cyclic structure with various ring size with adjacent quaternary/tertiary centers could be accessed in good yield with no erosion of the diastereoselectivity or the enantioselectivity **2a-c** (Scheme 9). Similarly when the terminal double bond aliphatic chain is situated on the benzylic position the treatment of the catalysis adduct with 5 mol % Grubbs second generation catalyst in refluxing dichloromethane provided enantioenriched cyclopentene, cyclohexene, cycloheptene bearing adjacent quaternary/tertiary centers in good yield with no erosion of the diastereoselectivity or the enantioselectivity **2d-f** (Scheme 9).



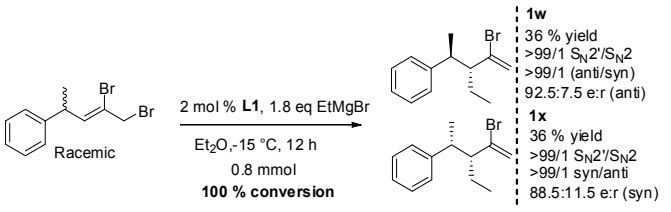
Scheme 9: Ring closing metathesis.

The formation of contiguous tertiary/tertiary stereocenters was tested with the best experimental conditions (Scheme 10) for product **1v**. We were pleased to get the expected high ee values. However, the anti/syn ratio was not perfect; a 8.5/1 ratio was obtained in favour of the anti diastereoisomer. This indicates that a partial ligand control operates in this case. Interestingly, when the starting material is recovered in 40 % yield with 85 % ee) and the same reaction was performed under copper/phosphoramidite conditions. The same ee value was obtained, except that the anti/syn ration dropped to 2.8/1 ratio. In both cases this is unfortunate because the anti/syn diastereomers are unseparable by SiO_2 chromatography. The **L1** was found out to be more efficient than **L4** for this substrate. It should be noted that in the case of tertiary/tertiary stereocenters, it was expected to get high gamma regioselectivity under Cu catalysis [19].



Scheme 10: Outlook: Single vessel reaction to generate vicinal tertiary stereocenters via kinetic resolution. Absolute configuration determination [20].

The unexpected partial ligand control finds its summit in the case depected in Scheme 11. When the reaction is pushed to 100% conversion each enantiomer of the racemic starting material reacted differently to afford diastereoisomers **1w** and **1x** separable by column chromatography. This parallel kinetic resolution [21] is possible by an impressive ligand control in contrast to the construction of tertiary/quaternary pattern (substrate control in this case). Again the **L1** was found out to be more efficient than **L4** for this substrate.



Scheme 11: Outlook: Single vessel reaction to generate vicinal tertiary stereocenters via parallel kinetic resolution. Absolute configuration determination [22].

Conclusions

The first transition metal free diastereoselective and enantioselective AAA has been disclosed leading to the construction of vicinal tertiary/quaternary centers via a kinetic resolution protocol. Crucially this is the first report in the AAA including metal catalyzed process that an additional racemic sterocenter in the substrate can be employed to afford the

construction of two stereocenters in a single vessel reaction. It is crucial to take into account that the additional steric hindrance added by the presence of the stereocenter in the substrate is extremely challenging. Therefore the use of a catalyst able to promote in high fashion the regioselectivity, diastereoselectivity and enantioselectivity remained undisclosed in the literature. A large range of Grignard reagents and a wide substrate scope could be employed, delivering the desired adducts with high regioselectivity, diastereoselectivity, enantioselectivity and good overall yield. Simple derivatizations were performed to give access to interesting and challenging synthons This procedure is chemically appealing since no consecutive AAA or stereoselective metal catalyzed AAA are required to construct the two stereocenters as previously reported in the literature. In addition the absence of a transition metal is interesting in terms of costs and generation of less toxic waste. Another blatant advantage is the ease of preparation of the starting materials (two steps).

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