Asymmetric Catalysis

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# Identification of a Valuable Kinetic Process in Copper-Catalyzed Asymmetric Allylic Alkylation**

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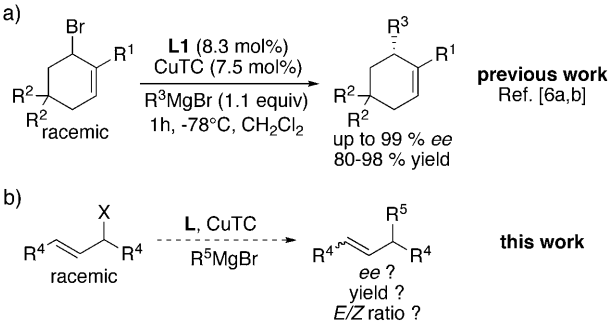
Since the past decade, copper-catalyzed asymmetric allylic alkylation has attracted the interest of many research groups, and such groups have succeeded in considerably extending the range of applications as well as the efficiency of this reaction.[1] Prochiral substrates are generally used, thus providing versatile chiral synthons stemming from a selective $S_N2'$ displacement of the leaving group.[2] Because of this particular feature, chemists rarely studied racemic substrates as an *anti* $S_N2'$ process would lead to racemic products. However, the few investigations on the reactivity of this class of substrates gave rise to the development of outstanding processes that significantly contributed to the understanding of the reaction.[3] In 1998, Pineschi, Feringa, and co-workers achieved pioneering work in this field with the kinetic resolution of cycloalkadiene monoepoxide in the presence of chiral phosphoramidite ligands.[4] A few years later, the same groups established that the enantiomers of the racemic allylic epoxide might have different reactivity under the reaction conditions and that they could be selectively transformed into two distinct regioisomers (regiodivergent kinetic resolution).[5] Recently, our group reported on the development of a dynamic kinetic asymmetric transformation (DYKAT).[6] Such a process used the difference in reactivity of the enantiomers of a racemic substrate to quantitatively form a unique enantioenriched product (up to 99% *ee*; Scheme 1a). From a synthetic point of view, this reaction constitutes a significant achievement considering the complete conversion of the starting material as well as the formation of a unique isomer of the alkylation product. Notwithstanding, the reaction proved to be effective only on 3-bromocyclohexene derivatives and this lack of generality limited its application in organic synthesis. To address this problem, the reactivity of acyclic racemic substrates should be studied (Scheme 1b). Herein, we present our findings on the difficulty of performing a DYKAT process on acyclic substrates and how the conformational flexibility of these substrates led us to unveil a new and valuable process for copper-catalyzed asymmetric allylic alkylation.




***Scheme 1.*** Evaluation of acyclic allylic halides as candidates for a dynamic kinetic asymmetric transformation.

Our investigations started with the reaction of (*E*)-4-bromopent-2-ene (**1**)[7] with phenethylmagnesium bromide in dichloromethane at −78 °C. In using the reaction conditions previously described for the DYKAT,[6a,b] a combination of CuTC (copper (I) thiophenecarboxylate) and the phosphoramidite ligand **L1** was chosen as the catalyst. This attempt quantitatively afforded the alkylation product **3** albeit as an inseparable mixture of *E* and *Z* stereoisomers (Table 1, entry 1). Interestingly, we noticed that both isomers of **3** were isolated in promising enantiomeric excesses of 72 and 66%, respectively. The use of ligands **L2** and **L3** failed to improve this result even though a slight preference for the *Z* isomer was observed (entries 2 and 3). Better enantioselectivities and an *E*/*Z* ratio of 45:55 were obtained when the sterically hindered ligand **L4** was used (entry 4). Performing the reaction with (*E*)-4-chloropent-2-ene (**2**) led to a significant increase of the *ee* values to 84 and 81% (entry 5).[8] Furthermore, improvement of the enantioselectivity was achieved when the Grignard reagent was added over a period of 30 minutes (entry 6).[9] Thus, the alkylation product **3** was obtained as an equimolar mixture of the *E* and *Z* isomers in 90 and 88% *ee*, respectively.

Goering and co-workers have demonstrated that a significant amount of the *Z* adduct could be formed in the alkylation of various *E*-allylic substrates by using an organocopper reagent, but never as an equimolar mixture with the *E* adduct.[10] This specific feature strongly compromised the development of a DYKAT, wherein the alkylation product should be recovered as a single isomer.[6c,d] However, the high level of enantioinduction observed for each isomer prompted us to get more insight into the reaction mechanism.

The product mixture obtained from the reaction listed in entry 6 of Table 1 was submitted to ozonolysis and subsequent reduction using $NaBH_4$ (Scheme 2). (*R*)-2-methyl-4-phenyl-

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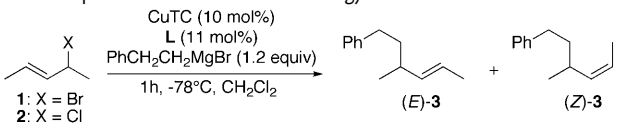
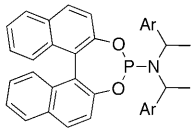
***Table 1:*** Optimization of the methodology.[a]

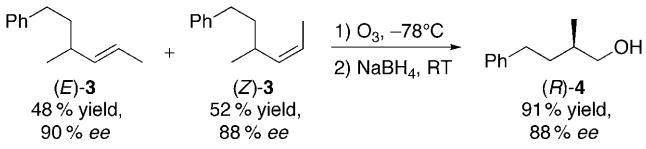


**L1**: $S_a,S,S$, Ar = Ph;
**L2**: $R_a,S,S$, Ar = Ph;
**L3**: $R_a,S,S$, Ar = *o*-MeOC$_6$H$_4$;
**L4**: $R_a,R,R$, Ar = 2-Naphth

| Entry | Substrate | Ligand | Conv. [%][b] | $E/Z$[c] | *ee* [%][d] | |
|---|---|---|---|---|---|---|
| | | | | | (*E*)-**3** | (*Z*)-**3** |
| 1 | **1** | **L1** | >99 | 44:56 | 72 | 66 |
| 2 | **1** | **L2** | >99 | 37:63 | 72 | 54 |
| 3 | **1** | **L3** | >99 | 35:65 | 66 | 42 |
| 4 | **1** | **L4** | >99 | 45:55 | 76 | 74 |
| 5 | **2** | **L4** | >99 | 47:53 | 84 | 81 |
| 6[e] | **2** | **L4** | >99 | 48:52 | 90 | 88 |

[a] Reaction conditions: The racemic substrate (0.25 mmol) was added to a solution of CuTC (10 mol%) and ligand (11 mol%) in dry $CH_2Cl_2$ at −78°C. The Grignard reagent (1 M in $Et_2O$, 1.2 equiv) was added dropwise and the reaction mixture was stirred for 1 h. The sterochemical descriptors $R_a$ and $S_a$ used for ligands **L1**–**L4** refer to the axial chirality. [b] Conversion relative to the formation of product **3**, determined by GC–MS analysis. [c] Determined by $^1$H NMR analysis. [d] Determined by GC analysis using a chiral stationary phase. [e] The Grignard reagent was added over 30 min. Naphth = naphthyl.

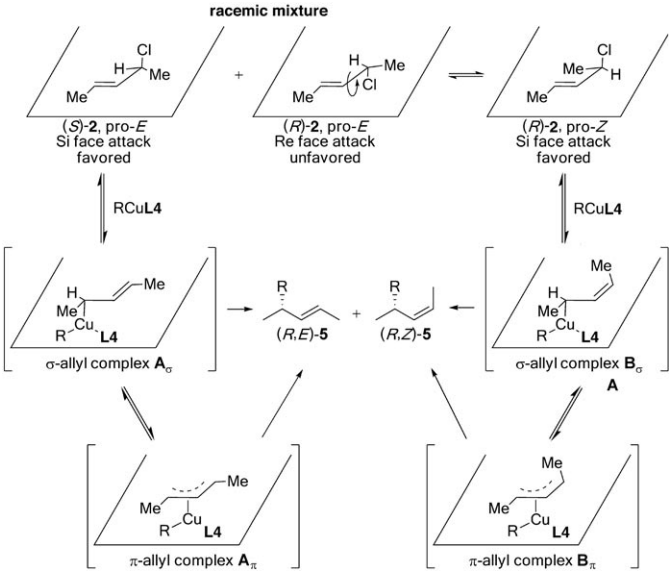



***Scheme 2.*** Identification of the process.

butanol (**4**) was isolated in 91% yield and 88% *ee* indicating that both isomers of **3** possess the same absolute configuration. This observation strongly suggested that the adducts arise from an attack on the same enantiotopic face of the starting material given that such a product distribution could be hardly attained by equilibrium between the σ- and π-allyl species. In addition, the small difference in energy between the conformers of **2** ($\Delta E_2 = 1.14$ kcal mol$^{-1}$) certainly facilitated their equilibration allowing the organocopper reagent to attack either the pro-*E* or the pro-*Z* conformers.[11] Obtaining two distinct enantioenriched isomers of the alkylation product encouraged us to consider the possibility of a parallel kinetic resolution process (PKR).[12] In 1967, Guetté and Horeau developed a simple equation based on the respective proportions and optical purities of each adduct obtained in a PKR reaction [Eq. (1)].[13] Thus, at full conversion the relationship between the isomers of **3** should be equal to the value of the initial enantiomeric excess of the

$$ee_{(Z)\text{-}\mathbf{3}} \times [(Z)\text{-}\mathbf{3}] - ee_{(E)\text{-}\mathbf{3}} \times [(E)\text{-}\mathbf{3}] = ee_{\mathbf{2}\text{initial}} \quad (1)$$

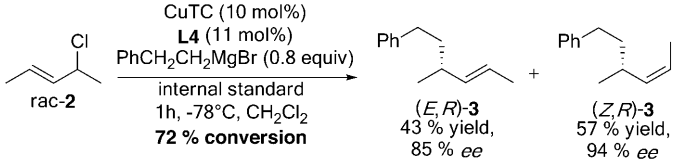
starting material. In the present case, the calculated value of $ee_{\mathbf{2}\text{initial}}$ was found to be inferior to 3%, which was consistent with the use of a racemic substrate.[14] Based on these results and observations, we postulated a reaction mechanism (Scheme 3).



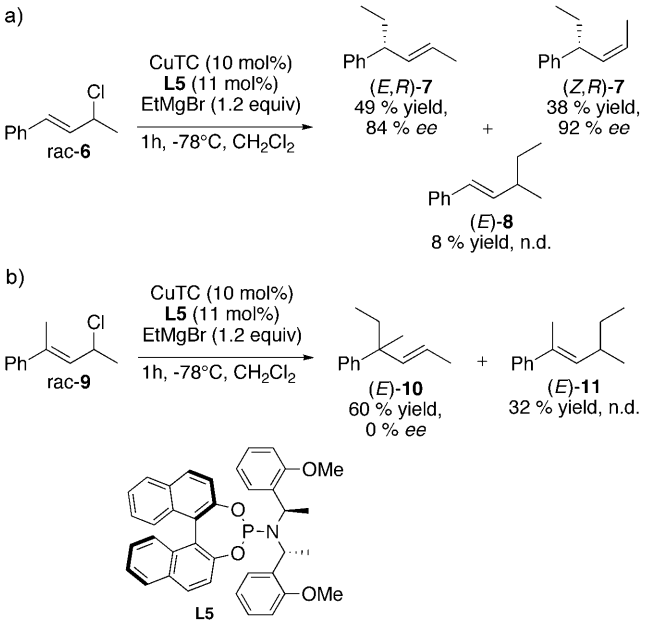

***Scheme 3.*** Plausible reaction mechanism.

Some prerequisites are needed to better understand the reaction pathway: 1) the reactivity of each enantiomer of the allylic chloride **2** has to be distinguished, 2) as mentioned, the reactivity of the organocopper species implies an *anti*-$S_N2'$ displacement of the leaving group,[2] and 3) the chiral catalyst induces a selective attack on one enantiotopic face of the disubstituted olefin, that is, the Si face given the observed absolute configuration of the alkylation products. The facial selectivity might be ascribed to steric interactions between the chiral ligand and the vinylic methyl group but the difficulty in obtaining a crystal structure of the catalyst prevented us from asserting exactly which interactions governed the facial selectivity. Thus, (*S*)-**2** is perfectly disposed to undergo an oxidative addition from its pro-*E* conformer, leading to the (*E*)-σ-allyl intermediate $\mathbf{A}_\sigma$. Subsequent reductive elimination, either directly or through the π-allyl complex $\mathbf{A}_\pi$, will selectively afford the *E* isomer of the alkylation product **5**. In sharp contrast, an *anti* attack on the pro-*E* conformer of (*R*)-**2** would involve the approach of the chiral catalyst on the Re face of the olefin. This possibility would be considerably disfavored but the conformational flexibility offered by an acyclic system allowed a rotation around the C3–C4 bond, leading to the pro-*Z* conformer of the substrate. The latter could be attacked on the Si enantiotopic face providing (*Z*)-σ-allyl intermediate $\mathbf{B}_\sigma$, then a possible π-allyl complex $\mathbf{B}_\pi$, and finally (*Z*)-**5** after reductive elimination. Interestingly, when the reaction was stopped at 72% conversion, a 43:57 mixture of the *E*/*Z* isomers of **3** was recovered, indicating a slight kinetic preference for the formation of the *Z* isomer (Scheme 4). This observation means that the rotation




***Scheme 4.*** Control experiment.




***Scheme 5.*** Use of unsymmetrical substrates. n.d. = not determined

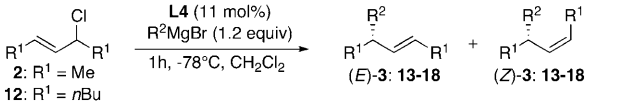
required for the formation of this stereoisomer did not slow down the reactivity of (*R*)-**2** and that the system could easily make up for this expense of energy if the approach of the chiral catalyst is facilitated. This mechanism represents the first example of stereodivergent kinetic resolution (SKR) in copper-catalyzed asymmetric allylic alkylation.[15]

Having established a plausible reaction pathway, a specific aspect remains intriguing: the formation of a π-allyl intermediate is neither stereo- nor enantiodetermining in the proposed mechanism.[16] In contrast to cyclic systems, it could be assumed that the flexibility of acyclic substrates may allow preorganization of the system before the key oxidative addition step. Thus, in the present case and in opposition to the DYKAT process, the enantio-, stereo- and regioselections are determined before the possible formation of a π-allyl moiety, thereby rendering its involvement only formal.

This particular feature might be exemplified by the application of the process to unsymmetrical substrates. Unfortunately, the preparation of the regioisomerically pure unsymmetrical secondary allylic chlorides remains a difficult challenge in organic synthesis.[17] (*E*)-(3-chlorobut-1-en-1-yl)benzene (**6**) was a rare exception and has been synthesized as a unique isomer.[18] To our delight, the alkylation reaction gave the $S_N2'$ adduct **7** as the major product (**7**/**8** 92:8) and as a mixture of *E* and *Z* stereoisomers in 84 and 92% *ee*, respectively (Scheme 5a). Importantly, a different chiral ligand, **L5**, was needed owing to the significant structural modification of the substrate.[19] Interestingly, when substrate **9** was submitted to the reaction conditions, (*E*)-**10** was obtained as the sole $S_N2'$ stereoisomer albeit in a racemic form (Scheme 5b). This result could be explained by a strong 1,3-allylic strain destabilizing the pro-*Z* conformer of **9** (Me–Me interaction, $\Delta E_9 = 5.10$ kcal mol$^{-1}$) and leading exclusively to the formation of the racemic *E*-adduct **10**.[20] The larger proportion of the $S_N2$ adduct **11** formed in this reaction could be ascribed to the propensity of the system to release the strain induced by the formation of a quaternary center.

The generality of the reaction was finally explored using the readily accessible model substrate **2** and various Grignard reagents (Table 2). The introduction of homoprenyl group was achieved with rigorously the same efficiency than the model phenethyl group, affording the product **13** in 92% yield (isolated) and *ee* values of 90 and 88% (entries 1 and 2, Table 2). The addition of dodecylmagnesium bromide provided **14** in high yield and in about 90% *ee* (entry 3). (*R*,*E*)- and (*R*,*Z*)-8-(*tert*-butoxy)-4-methyloct-2-ene (**15**) were obtained in good yield and as an equimolar mixture. Surprisingly, the *E* isomer was isolated with lower asymmetric induction than the *Z* isomer (74 and 88% *ee*, respectively; entry 4). Cyclohexylmagnesium bromide proved to react in the same manner as the primary alkyl Grignard reagents albeit in lower enantioselectivity (entry 5). In stark contrast, phenylmagnesium bromide displayed a totally different reactivity, leading to racemic (*E*)-pent-3-en-2-ylbenzene (**17**) in good stereoselectivity (entry 6).[21] Finally, (*E*)-7-chloroundec-5-ene (**12**) showed a similar reactivity and adducts **18** were recovered in 95% yield and 88% *ee* (entry 7).[22]

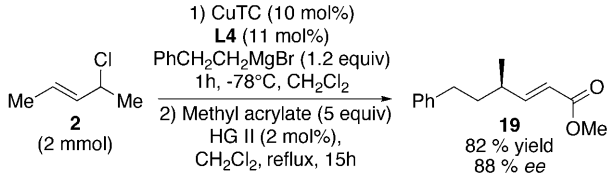
***Table 2:*** Generality of the reaction.[a]




| Entry | Substr. | $R^2$ | Prod. | Yield [%][b] | *E*/*Z*[c] | *ee* [%][d] $ee_E$ | $ee_Z$ |
|---|---|---|---|---|---|---|---|
| 1 | **2** | $PhCH_2CH_2$ | **3** | 85 | 48:52 | 90 | 88 |
| 2 | **2** | $(CH_3)_2C{=}CHCH_2CH_2$ | **13** | 92 | 48:52 | 90 | 88 |
| 3 | **2** | $C_{12}H_{25}$ | **14** | 97 | 44:56 | 89 | 91 |
| 4 | **2** | $tBuO(CH_2)_4$ | **15** | 91 | 49:51 | 74 | 88 |
| 5 | **2** | Cy | **16** | 87 | 48:52 | 80 | 76 |
| 6 | **2** | Ph | **17** | 85 | 93:7 | 0 | 0 |
| 7 | **12** | $PhCH_2CH_2$ | **18** | 95 | 48:52 | 88[f] | – |

[a] Reaction conditions: The racemic substrate (0.25 mmol) was added to a solution of CuTC (10 mol%) and **L4** (11 mol%) in dry $CH_2Cl_2$ at −78 °C. The Grignard reagent (1 M in $Et_2O$, 1.2 equiv) was added over 30 min and the reaction mixture was stirred for 1 h. [b] Yield of isolated mixture of *E* and *Z* products. [c] Determined by $^1$H NMR analysis. [d] Determined by GC analysis using a chiral stationary phase. [e] Determined by supercritical fluid chromatography (SFC) analysis using a chiral stationary phase. Material used was obtained from the reaction sequence described in Scheme 2a. Cy = cyclohexyl.

In addition to mechanistic interest, the process reported herein could be a valuable tool for organic synthesis. Simple transformations such as ozonolysis, hydrogenation, or cross-metathesis might erase the dichotomy between the stereoisomers of the alkylation product and quantitatively afford a single enantioenriched compound. For instance, (*E*)- and (*Z*)-**3** were prepared on a synthetically useful scale (2 mmol) using the SKR process and subsequently reacted with methyl acrylate in the presence of the second-generation Hoveyda–Grubbs catalyst (Scheme 6).[23] (*E*)-α,β-unsaturated ester (**19**)




***Scheme 6.*** Scale-up preparation and derivatization of adducts **3**. HG II = Hoveyda–Grubbs second-generation catalyst.

was isolated as the sole stereoisomer in 82% yield and 88% *ee*.[24]

In conclusion, acyclic allylic systems have shown a fundamentally different reactivity profile compared to cyclic substrates, which precluded the development of a DYKAT. However, the conformational flexibility of this class of substrates allowed us to identify a highly enantioselective stereodivergent kinetic resolution (up to 91% *ee*). Such a process is rare in transition-metal catalysis and unprecedented in copper chemistry. Studies are currently ongoing in our laboratory to extend our comprehension of the system and particularly to understand the striking difference between DYKAT and SKR processes towards the influence of a π-allyl intermediate on the reaction outcome.

## *Experimental Section*

In a flame-dried Schlenk tube an under nitrogen atmosphere, CuTC (4.8 mg, 0.025 mmol, 0.1 equiv) and **L4** (17.6 mg, 0.028 mmol, 0.11 equiv) were dissolved in dry $CH_2Cl_2$ (2 mL) and the solution was stirred for 10 min at room temperature. The reaction mixture was then cooled to −78 °C and the freshly prepared substrate (0.25 mmol) was added. After 10 min at this temperature, the Grignard reagent (1M in $Et_2O$, 0.3 mL, 0.3 mmol, 1.2 equiv) was added over 30 min and the reaction mixture was stirred for 1 h. The reaction was quenched with HCl 1M (5 mL) and extracted with diethyl ether (3 × 5 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under vacuum. The crude reaction mixture was purified by chromatography on silica gel (*n*-pentane) and the desired product (up to 97%) was recovered as a colorless liquid. For additional details, see the Supporting Information.

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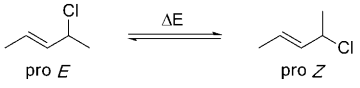
[11] $\Delta E_2$ represents the difference in energy between the conformers of substrate **2**. The value has been calculated with Gaussian 03 using MP2/6-311G**//PBE1PBE/6-311G** methods. See the Supporting Information for experimental details.

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[22] (*E*)-5-chloro-2,6-dimethylhept-3-ene and (*E*)-5-chloro-2,2,6,6-tetramethylhept-3-ene have been evaluated in the reaction conditions. Unfortunately, an undesired elimination reaction leading to the formation of a diene and a lack of reactivity were respectively observed.
[23] For previous examples of copper-catalyzed asymmetric allylic alkylation/cross-metathesis sequences involving an acrylate as a coupling partner, see: a) A. Alexakis, K. Croset, *Org. Lett.* **2002**, *4*, 4147; b) M. A. Kacprzynski, T. L. May, S. A. Kazane, A. H. Hoveyda, *Angew. Chem.* **2007**, *119*, 4638; *Angew. Chem. Int. Ed.* **2007**, *46*, 4554; c) A. W. van Zijl, W. Szymanski, F. Lopez, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2008**, *73*, 6994.
[24] This SKR/cross-metathesis sequence could be particularly interesting since the copper-catalyzed asymmetric allylic alkylation of crotyl chloride remained a preeminent challenge in this field, affording after extensive optimizations only 80% *ee* for the γ-alkylated product.