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Dynamic kinetic asymmetric transformation in copper catalyzed allylic alkylation†‡

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The first dynamic kinetic asymmetric transformation in copper catalyzed allylic alkylation is reported, with enantioselectivities up to 92%.

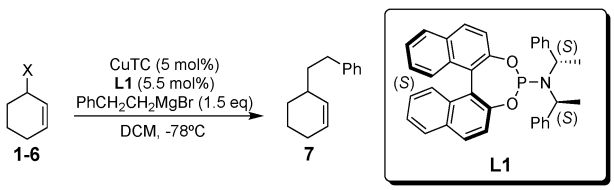
At the end of the 90s, Trost introduced the concept of dynamic kinetic asymmetric transformation (DYKAT) in allylic substitution.[1] This represents one of the most efficient methodologies for the transformation of a racemic substrate in an enantio-enriched product.[2] The concept was applied to palladium catalyzed asymmetric allylic alkylation (AAA) using stabilized nucleophiles.[3] However, to the best of our knowledge, only a few examples were described using non-stabilized nucleophiles. Some advances in this field were achieved in nickel catalysis. Consiglio and co-workers described the alkylation of cyclic allylic ethers by EtMgBr affording quantitatively alkylated products in high enantioselectivity (up to 93% ee).[4,5] Recently Fu and co-workers reported the alkylation of acyclic allylic chlorides with organozinc reagents with ee up to 98%.[6] Surprisingly, although copper is one of the most efficient transition metals to form enantioselectively an allylic C–C bond using non-stabilized nucleophiles,[7] no examples of DYKAT in copper catalysis have been reported to date. In 2007, Bäckvall described a copper catalyzed racemisation of enantiopure allylic acetates, demonstrating that a DYKAT was envisageable in this chemistry.[8] In this context it was interesting to develop an efficient dynamic process in copper catalysis. We report herein our investigations in this field.

We started our study with the reaction of cyclohex-1-enyl-3-acetate **1** and phenethylmagnesium bromide in CH_2Cl_2 (Table 1). Using copper(I) thiophene-2-carboxylate (CuTC, 5 mol%) and **L1** (5.5 mol%) at −78 °C, the product was obtained quantitatively, albeit in racemic form (entry 1, Table 1). Other leaving groups such as carbonate **2** and phosphonite **3** were tested, resulting in low but measurable enantiomeric excesses (entries 2 and 3). A large improvement in enantioselectivity was attained with chloride **4** and bromide **5**, which provided the product (*S*)-**7** with 53 and 78% ee, respectively (entries 4 and 5). The formation of the product was not observed with triflate **6**, probably due to a competitive elimination reaction (entry 6). Clearly, the enantioselectivity is intimately linked to the leaving group ability of X (Br ≫ Cl ≫ $OP(O)Ph_2$ > OCO_2Me > OAc). This result prompted us to further optimize the process using model substrate **5**.

Although various ligands were tested in this reaction, **L1** was found to be the most effective (entry 1, Table 2). The use of ligand **L2** (Fig. 1) led to a mismatch situation (18% ee; entry 2).[9] It is worth noting that the absolute configuration of the adduct remains the same. A similar situation was observed with ligands **L3** and **L4**, which afforded product **7** in 32 and 76% ee, respectively (entries 3 and 4). Ligand **L5**, having a naphthylethylamine group, gave a comparable result to **L1** and **L4** (entry 5). Tropos ligand[10] **L6** and Simplephos ligand[11] **L7** failed to improve this result and poor enantioselectivities were obtained (entries 6 and 7). Low reactivity was observed with Taniaphos ligand **L8** (entry 8). Almost no enantioinduction was obtained using carbene ligand precursor **L9** (entry 9).[12]

Keeping **L1** as ligand, different solvents were screened. Coordinating solvents, such as diethyl ether (Et_2O) and tetrahydrofuran (THF), led to the formation of product **7** as a racemate (entries 10 and 11). Dichloromethane appeared to be the solvent of choice for this reaction (entry 1). Lowering the reaction concentration from 0.18 M to 0.1 M enhanced the enantioselectivity to 86% ee (entry 12). A concentration of 0.07 M did not further improve this result (entry 13), suggesting that a precise quantity of CH_2Cl_2 was needed to reduce the

Table 1 Screening of different leaving groups[a]



Entry	X	Substrate	*t*/h	Conversion (%)[b]	ee (%)[c]
1	OAc	**1**	15	83	0
2	OCO_2Me	**2**	15	83	4 (*S*)
3	$OP(O)Ph_2$	**3**	3	>99	8 (*S*)
4	Cl	**4**	2	>99	53 (*S*)
5	Br	**5**	1	>99	78 (*S*)
6	OTf	**6**	1	0[d]	—[d]

[a] Reaction conditions: Racemic substrate (0.5 mmol) was added to a solution of CuTC and **L1** in dry CH_2Cl_2 (2 ml). The reaction mixture was cooled to −78 °C and the Grignard reagent (1 M in Et_2O) was added dropwise. [b] Conversion relative to the formation of **7**, determined by GC-MS. [c] Determined by GC on chiral stationary phase. [d] The formation of **7** was not observed.

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‡ Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b907722g

Table 2 Screening of chiral ligands and solvents[a]

Entry	Ligands	Solvent	Conversion (%)[b]	ee (%)[c]
1	**L1**	CH_2Cl_2	>99	78 (*S*)
2	**L2**	CH_2Cl_2	>99	18 (*S*)
3	**L3**	CH_2Cl_2	>99	32 (*S*)
4	**L4**	CH_2Cl_2	>99	76 (*S*)
5	**L5**	CH_2Cl_2	>99	78 (*R*)
6	**L6**	CH_2Cl_2	>99	4 (*S*)
7	**L7**	CH_2Cl_2	>99	8 (*S*)
8	**L8**	CH_2Cl_2	8	n.d.[d]
9	**L9**[e]	CH_2Cl_2	>99	2 (*R*)
10	**L1**	Et_2O	>99	0
11	**L1**	THF	>99	0
12	**L1**	CH_2Cl_2[f]	>99	86 (*S*)
13	**L1**	CH_2Cl_2[g]	>99	86 (*S*)
14	**L1**[h]	CH_2Cl_2[f]	>99	92 (*S*)

[a] Reaction conditions: Racemic substrate **5** (0.5 mmol) was added to a solution of CuTC (5 mol%) and chiral ligand (5.5 mol%) in dry solvent (2 ml). The reaction mixture was cooled to −78 °C and the Grignard reagent (1 M in Et_2O, 1.5 equiv.) was added dropwise. [b] Conversion determined by GC-MS. [c] Determined by GC on a chiral stationary phase. [d] Not determined. [e] Carbene ligand was formed *in situ* by addition of *n*-BuLi. [f] 0.1 M in **5**. [g] 0.07 M in **5**. [h] 7.5 mol% catalyst loading.

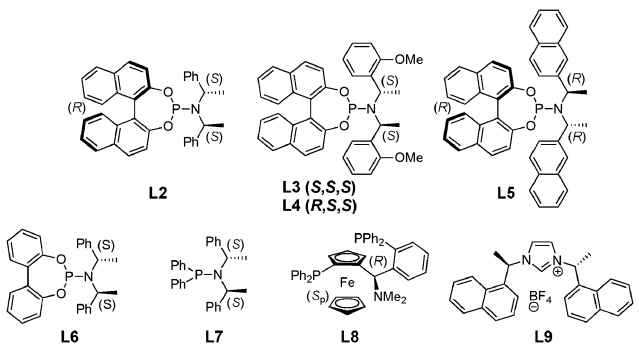


Fig. 1 Chiral ligands.

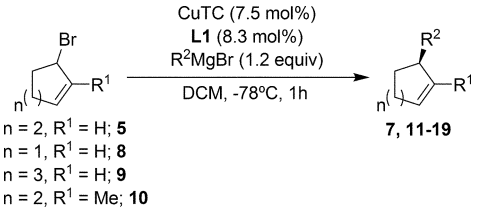
possible coordination of ether (contained in the Grignard solution) to the metal.[13]

The nature of the copper source does not have a notable influence on the selectivity of the reaction except for copper cyanide and copper triflate which gave lower ee's (see Supporting Information‡).[14]

Increasing the catalyst loading from 5 mol% to 7.5 mol% avoided an erosion of the enantiomeric excess during the course of the reaction and 92% ee was attained (entry 14, Table 2; see Supporting Information‡). The use of organozinc reagents,[15] instead of Grignard reagents, led to the same enantiomeric excess (see Supporting Information‡).

With these conditions in hand, the scope of Grignard reagents was studied in order to test the generality of this method (Table 3).§ The process was found to be very efficient with primary alkyl Grignard reagents which always gave excellent ee's ranging from 90 to 92% (entries 1 to 4, Table 3). A lower enantioselectivity was observed with secondary and tertiary alkyl Grignard reagents. Indeed, 3-cyclohexylcyclohex-1-ene **14** and 3-*tert*-butylcyclohex-1-ene **15** were isolated with 70 and 50% ee, respectively (entries 5 and 6). The use of phenyl Grignard reagent afforded product

Table 3 Scope of the process[a]

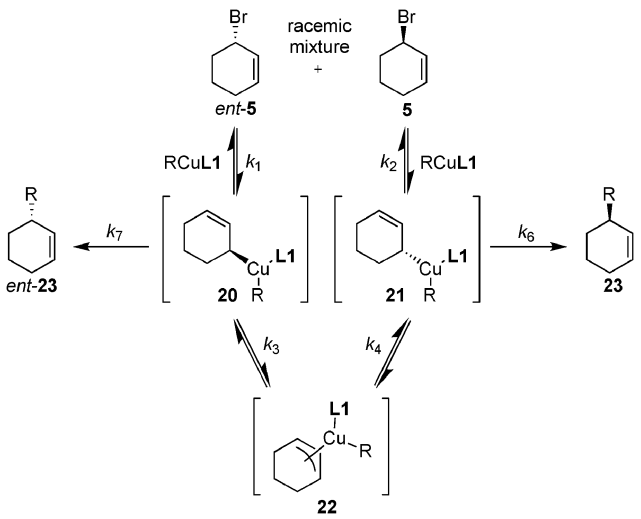


Entry	Substrate	R^2	Product	Yield (%)[b]	ee (%)[d]
1	**5**	$PhCH_2CH_2$-	**7**	95	92 (*S*)
2	**5**	Et-	**11**	79[c]	90 (*R*)
3	**5**	*n*-Bu-	**12**	81[c]	92 (*R*)
4	**5**	*t*-BuOBu-	**13**	91	90 (*S*)
5	**5**	Cy-	**14**	98	70 (*S*)
6	**5**	*t*-Bu-	**15**	80[c]	50 (*R*)
7	**5**	Ph-	**16**	97	0[e]
8	**8**	$PhCH_2CH_2$-	**17**	93	44 (*S*)
9	**9**	$PhCH_2CH_2$-	**18**	98	38 (*S*)
10	**10**	$PhCH_2CH_2$-	**19**	95	18 (*S*)

[a] Reaction conditions: Racemic substrate (0.5 mmol) was added to a solution of CuTC and **L1** in dry CH_2Cl_2 (4 ml). The reaction mixture was cooled to −78 °C and the Grignard reagent was added dropwise. [b] Yield of isolated product. [c] Isolated yield of the corresponding diastereomeric epoxides obtained by treatment with mCPBA. [d] Determined by GC on a chiral stationary phase after derivatization of a sample of the isolated product into the corresponding epoxides. [e] Determined by SFC on chiral stationary phase.

16 as a racemate (entry 7). Other cyclic substrates were surveyed. Cyclopent-1-enyl-3-bromide **8** and cyclohept-1-enyl-3-bromide **9** afforded products **17** and **18** in 44 and 38% ee, respectively (entries 8 and 9). 18% ee was also obtained with 1-methylcyclohex-1-enyl-6-bromide **19** (entry 10).

Based on these results, we propose a plausible reaction mechanism (Scheme 1). The first step is the ionization of the substrate by insertion of the metal into the allylic terminus (oxidative addition) and the last is the reductive elimination leading to a mixture of products **23** and *ent*-**23**. During these two steps, the σ-allyl species **20** and **21**, stemming from the



Scheme 1 Proposed mechanism for the DYKAT of racemic substrate **5** (R = alkyl or aryl group, *k* = equilibrium constant).

ionization of **5** and *ent*-**5**, are in equilibrium *via meso*-π-allyl complex **22**.[16] In the case of low reactive allylic acetates, Cu(III) intermediates are accepted to have a very short lifetime. Consequently, the ionization step is rate limiting (k_1, $k_2 \ll k_7$, k_6) and virtually no π-allyl equilibration takes place.[17] In the present case, allylic bromides are very reactive and Cu(III) intermediates presumably equilibrate *via* π-allyl intermediates of type **22**. Hence the reductive elimination step became rate determining (k_1, $k_2 \gg k_7$, k_6). Control experiments showed that the starting material **5** is racemic throughout the reaction (see Supporting Information‡), which is consistent with a dynamic process ($k_1 = k_2$). Ruling out the hypothesis of kinetic resolution implies that the enantiodiscrimination is due to a difference in the rate of the reductive elimination.[18] This difference displaces the equilibration of the intermediates through the formation of the product with the higher rate of elimination (*i.e.* if $k_6 > k_7$ the product will be enriched in **23**). This is consistent with the racemates obtained using coordinating solvents (entries 8 and 9, Table 2) where the reductive elimination is faster.[19] The same observation was made with the use of bulky R groups such as secondary and tertiary alkyl groups, which provided hindered allyl-intermediates favouring the elimination step (entries 5 and 6, Table 3).

In conclusion, despite a lack of generality, we have disclosed the first dynamic kinetic asymmetric transformation in copper catalyzed asymmetric allylic alkylation. This concept was applied to the alkylation of cyclohex-1-enyl-3-bromide **5** and was very efficient with primary alkyl Grignard reagents (ee's up to 92%). Work is in progress to widen the scope and the efficiency of the process.

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Notes and references

§ Representative procedure for copper catalyzed allylic alkylation (entry 1, Table 3): In a flame-dried Schlenk tube under argon atmosphere, CuTC (7.2 mg, 0.038 mmol, 0.075 equiv.) and **L1** (22.2 mg, 0.041 mmol, 0.083 equiv.) were dissolved in dry CH_2Cl_2 (4 ml) and the solution was stirred for 10 min at room temperature. Then the substrate **5** (80 mg, 0.5 mmol, 1 equiv.) was added and the solution was cooled to −78 °C. After 10 min at this temperature, the phenethylmagnesium bromide solution (1 M in Et_2O, 0.6 ml, 0.6 mmol, 1.2 equiv.) was added dropwise and the reaction mixture was stirred for 1 h. The reaction was quenched with an aqueous solution of 1 M HCl (15 ml) and extracted with Et_2O (15 ml). The organic layer was washed with 1 M HCl (15 ml) and brine (15 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified on a silica gel chromatography column (pentane) to afford product **7** (88 mg, 95%) as a colourless liquid. **7**: The enantiomeric excess was determined by GC on a chiral stationary phase (Hydrodex B3P column, Method: 60-30-1-140-20-170-5, R_T: 102.17 (*S*), 102.76 (*R*) min). The enantiomeric excess could also be determined after derivatization into the corresponding diastereomeric epoxides (Hydrodex TBDM column, Method: 60-0-1-170-5, R_T: 97.99, 99.01, 102.71, 104.25 min). $[\alpha]^{25}_D = -0.87$ ($c = 1.2$ in $CHCl_3$, 92% ee). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.34–1.37 (m, 1H), 1.59–1.81 (m, 4H), 1.89 (m, 1H), 2.06 (m, 2H), 2.18 (m, 1H), 2.74 (m, 2H), 5.71–5.76 (m, 2H), 7.25–7.35 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.6, 25.5, 29.2, 33.4, 34.9, 38.4, 125.8, 127.3, 128.4, 128.5, 131.9, 143 ppm. IR ($CHCl_3$): 71.9, 1453, 1493, 2856, 2923, 3023 cm^{-1}. MS (EI mode) *m*/*z* %: 186 (28), 143 (4), 129 (4), 104 (26), 91 (100), 65 (34), 53 (22). HRMS (ESI) calcd for $C_{14}H_{18}$ [M^+] 186.1409, found 186.1407.

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