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Cu-catalyzed asymmetric addition of sp^2-hybridized zirconium nucleophiles to racemic allyl bromides

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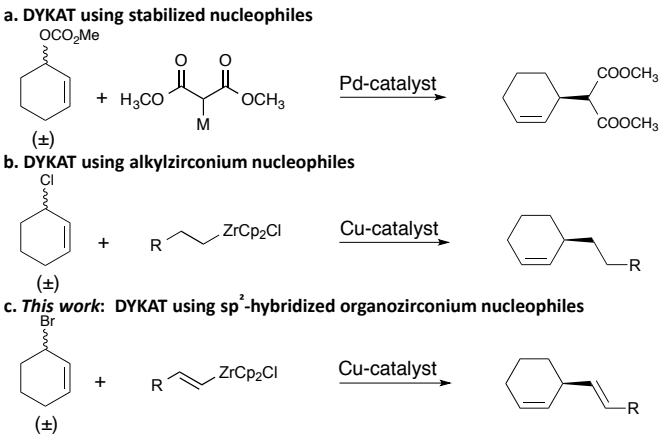
Alkenylzirconium nucleophiles made *in situ* by the hydrozirconation of terminal alkynes undergo dynamic kinetic asymmetric allylic alkenylation with racemic allyl bromides to give enantioenriched products.

Transition metal catalyzed asymmetric allylic alkylation (AAA) reactions have proven to be useful and versatile methods for C-C bond formation.[1] In particular, Pd-catalyzed AAAs in which enantiopure products are obtained from racemic mixtures of starting materials are exceptionally powerful and have been extensively developed.[2] The use of stabilized nucleophiles (pKa <25) in these processes is well-established (Figure 1a).[3,1b] These dynamic kinetic asymmetric transformations (DYKATs) convert both enantiomers of a starting material into one enantiomer of a new product without producing resolved starting material.[3,4] The use of non-stabilized nucleophiles in these procedures is much less developed – very few examples of relevant AAAs can be found in the literature.[5] Our group has developed highly enantioselective conjugate addition reactions using alkylzirconium reagents,[6] and recently reported Cu-catalyzed AAA of these nucleophiles to racemic cyclic allyl chlorides to give enantioenriched products (Figure 1b).[7]

To the best of our knowledge no AAAs have ever been reported using sp^2-hybridized nucleophiles in combination with chiral racemic starting materials, although Rh-catalyzed conjugate additions of boron-species are well-developed[8] and Cu-[9] and Ir-catalyzed[10] AAAs of vinyl-nucleophiles to prochiral substrates are known. Given our recent DYKATs with alkylzirconocene nucleophiles we speculated that this method may be extended to alkenylzirconocene reagents (Figure 1c) and here we report the exploration and optimization of this system.

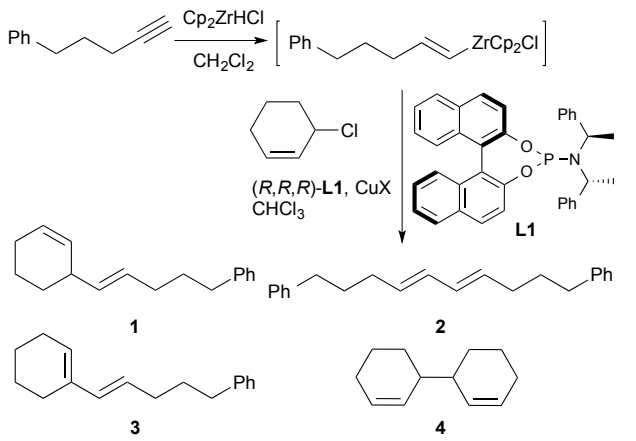
We began our studies using 5-phenyl-1-pentyne and 3-chlorocyclohex-1-ene. We first examined conditions previously optimised for AAAs using alkyl nucleophiles where a combination of CuI (10 mol%) and (*R*,*R*,*R*)-**L1** (10 mol%) were used in chloroform (Table 1, entry 1).[7] Under these conditions the starting material was nearly consumed, but no AAA product **1** was detected. Instead significant amounts of **2** (15%), arising from the dimerization of the alkenyl zirconocene, and **3** (6%), presumably from isomerization of **1**, were observed. We reasoned that other copper salts could favour the formation of **1** but found that $CuNTf_2$, CuOTf, $CuBF_4$, $CuSbF_6$ also mainly gave **2** as well as **4**, the homocoupled product of the starting allyl chloride (Table 1, entries 2-5). CuTC was found to give slightly lower conversion and the vinyl-dimer **2** as the major product in 20% yield (entry 6).

Figure 1. Dynamic Kinetic Asymmetric Allylic Alkylations



It appeared that dimerisation was significantly faster than AAA and we hypothesised that more reactive leaving groups could provide better results. Several cyclic allyl compounds bearing different leaving groups (Br, OAc, $O(CO)CF_3$, $OP(O)(OEt)_2$, OBoc) were examined using 10 mol% **L1** and CuI in chloroform and only the allyl bromide was found to give the desired product **1** in appreciable amounts.

Table 1. Selected screening reactions[a]

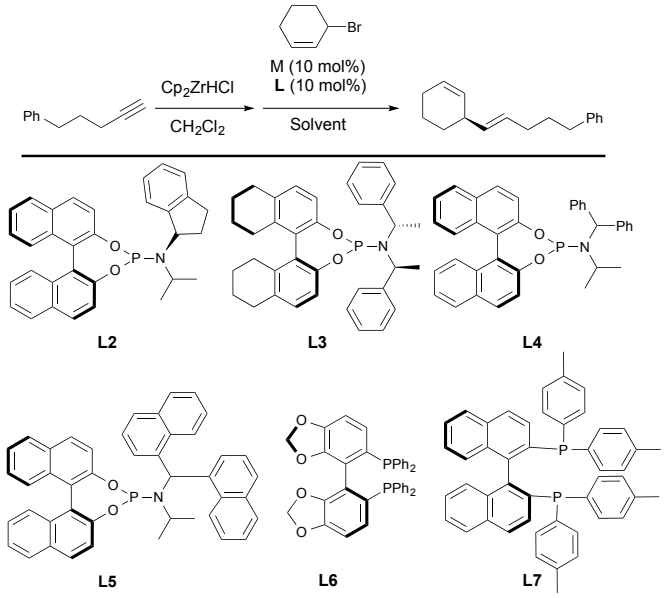


Entry	Cu(I)	Conversion[b] (%)	1 (%)	2 (%)	3 (%)	4 (%)
1	CuI	84	-	15	6	-
2	CuCl/AgNTf$_2$	100	-	43	8.4	14
3	CuCl/AgOTf	94	-	36	0	24
4	CuCl/AgBF$_4$	86	-	24	8.3	17
5	CuCl/AgSbF$_6$	92	-	23	8.4	20
6	CuTC	81	-	20	3.7	0

[a] Reaction conditions: 5-phenylpent-1-yne (2.5 eq), Cp$_2$ZrHCl (2.0 eq), CuI (10 mol%), (*R*,*R*,*R*)-**L1** (10 mol%) in chloroform. [b] Determined by proton NMR spectroscopy.

When using cyclohexenyl bromide and our standard conditions very low enantioselectivity (54:46 er, Table 2, entry 1) was obtained however only traces of diene **2** were observed. Several copper salts were employed using **L1** in CH_2Cl_2. Other copper halides did not improve the results (entries 2 and 3). The use of more reactive copper sources also provided very low enantiomeric ratios (entries 4-6). The role of the silver salt in these reactions is to exchange the counterion with CuCl. The use of CuTC and CuOTs (obtained premixing CuCl and AgOTs) gave slightly better er (entries 8 and 9). Using these copper sources several ligands were tested. **L2** gave an er of 74:26 with CuTC (entry 9) but with CuOTs the er was slightly lower (entry 10, 61:39) while **L3** gave better er both with CuTC and CuOTs (entries 11 and 12). **L4** and **L5**[6b] gave a lower er (entry 13 and 14) and other phosphoramidite ligands also did not give better results than **L3** (not shown). We also explored diphosphine ligands such as (*R*)-SegPhos (**L6**) and *p*-tol-BINAP **L7**. In these cases the yield dropped significantly although similar enantioselectivities were observed (entries 15 and 16). Using **L3** and CuOTs and changing the solvent did not improve enantioselectivities over those previously observed (entries 17-19). However, significant improvement was achieved by lowering the temperature to 0 °C (entry 20), and the best selectivity (81:19) was obtained at –40 °C (entry 21). Under these "optimized" conditions, **1** was obtained in 78% isolated yield. At lower temperatures, the er was comparable but the conversion dropped considerably.

Table 2. Optimisation of the reaction conditions[a]



Entry	M	Ligand	Solvent	Conversion (%)	er (%)
1	CuI	**L1**	$CHCl_3$	92[b]	54:46
2	CuCl	**L1**	CH_2Cl_2	81[b]	55:45
3	$CuCl_2$	**L1**	CH_2Cl_2	74[b]	50:50
4	CuCl+AgNTf$_2$	**L1**	CH_2Cl_2	100[b]	57:43
5	CuCl+AgBF$_4$	**L1**	CH_2Cl_2	93[c]	55:45
6	CuCl+AgOMs	**L1**	CH_2Cl_2	83[c]	60:40
7	CuTC	**L1**	CH_2Cl_2	79[c]	63:37
8	CuCl+AgOTs	**L1**	CH_2Cl_2	89[c]	65:35
9	CuTC	**L2**	CH_2Cl_2	90[c]	74:26
10	CuCl+AgOTs	**L2**	CH_2Cl_2	88[c]	61:39
11	CuTC	**L3**	CH_2Cl_2	94[c]	72:28
12	CuCl+AgOTs	**L3**	CH_2Cl_2	92[c]	76:24
13	CuTC	**L4**	CH_2Cl_2	87[c]	55:45
14	CuTC	**L5**	CH_2Cl_2	87[c]	56:44
15	CuCl+AgOTs	**L6**	CH_2Cl_2	33[c]	36:64
16	CuTC	**L7**	CH_2Cl_2	25[c]	66:34
17	CuCl+AgOTs	**L3**	Et_2O	30[c]	61:39
18	CuCl+AgOTs	**L3**	2-MeTHF	35[c]	61:39
19	CuCl+AgOTs	**L3**	Toluene	8[c]	67:33
20	CuCl+AgOTs	**L3**	CH_2Cl_2, 0 °C	90[c]	21:79[d]
21	CuCl+AgOTs	**L3**	CH_2Cl_2, –40 °C	90[c]	19:81[d]

[a] Reaction conditions: 5-phenylpent-1-yne (2.5 eq), Cp$_2$ZrHCl (2.0 eq), M (10 mol%), ligand (10 mol%) in chloroform. [b] Determined by NMR. [c] Determined by chiral HPLC. [d] Using (*R*,*R*,*R*)-**L3**.

When we attempted to explore the scope and limitations of this procedure it quickly became apparent that the use of

alkenyl nucleophiles in these hydrometallation AAA procedures was more challenging than initially expected. The AAA products are very non-polar making separation of the enantiomers by HPLC on a chiral non-racemic stationary phase complicated. Several simple linear alkynes were tested but it was difficult to find suitable analytical HPLC or GC methods for the products. In our previously reported AAAs (ref 7) we often measured the enantiomeric ratios of the cyclic products by epoxidation of the double bond. Epoxidation produced a diastereomeric mixture (a total of 4 isomers) but was found to make measurement of the isomer ratios much easier. In this case however, since the product contains two double bonds, epoxidation would give eight total stereoisomers complicating the analysis. An alternative way to establish the enantioselectivity (and overcome these analytical difficulties) would be to use an enantiomerically pure chiral alkyne, which would produce a diastereoisomeric mixture of products (Figure 2), and measure the resulting diastereomeric ratio (dr) by NMR spectroscopy to obtain the 'enantioselectivity'. We first prepared enantiomerically pure alkyne (*S*)-**5**, which undergoes non-selective allylic alkylation in the presence of stoichiometric CuBr.Me_2S to afford **6**. Unfortunately, all ^{13}C NMR (126 MHz) signals of diastereomers **6** almost completely overlap preventing meaningful dr determination. It was envisaged that use of a shorter chiral alkyne such as (*S*)-**7**[11] might overcome this problem. As shown in Figure 2 it is possible to clearly differentiate the diastereomers of **8** by ^{13}C NMR spectroscopy.

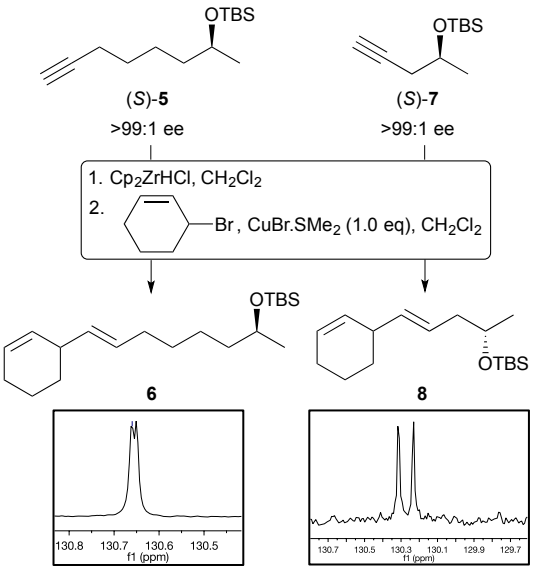
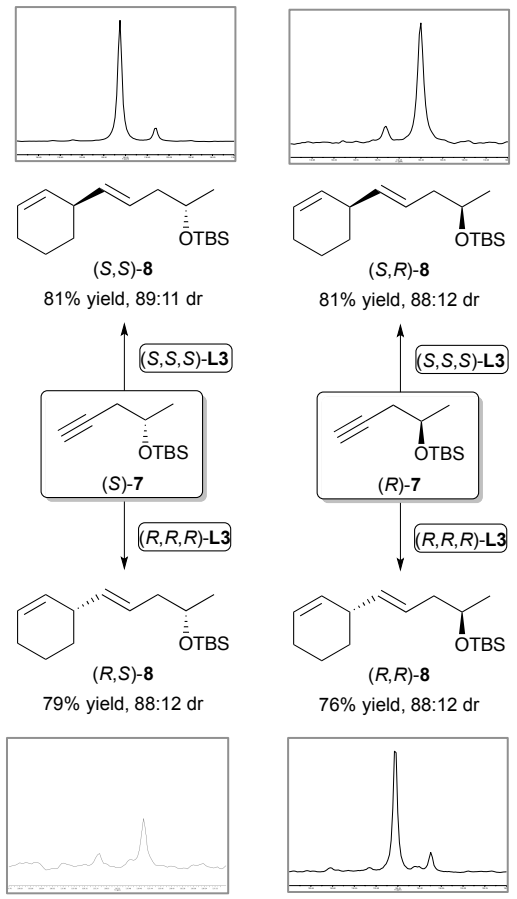


Figure 2. dr determination by ^{13}C NMR spectroscopy.

We prepared both enantiomers of alkyne **7** in enantiomerically pure form (>99:1 er) and subjected each of these to optimised AAA conditions using both enantiomers of **L3**. This gave all four possible stereoisomers as shown in Scheme 1. The configuration of the protected alcohol on the alkyne has no effect on the stereochemistry of the new C-C bonds so that stereoselectivity is entirely determined by the catalyst used. Here the yields are uniformly high and selectivity (usually 88:12 er) is higher than with the 5-phenyl-1-pentyne, which was used to optimize the system.

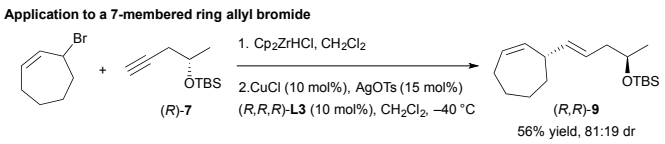
Scheme 1. Use of enantiopure chiral alkynes in dynamic kinetic asymmetric allylic alkenylation



Conditions: AAA of 3-bromo-1-cyclohexene (1.0 eq) using 2.5 eq of alkyne **7**, Cp_2ZrHCl (2.0 eq), CuCl (0.1 eq), AgOTs (0.11 eq) and **L3** (0.1 eq) in CH_2Cl_2 at –40 °C for 18 h.

A 7-membered ring product **9** was prepared using this procedure with a similar level of stereoselectivity (Scheme 2). We were unable to isolate 3-bromocyclopent-1-ene in high enough purity to test the reaction conditions on a five-membered ring.

Scheme 2. 7-membered ring example



In our previously reported AAAs (Figure 1b),[7] the mechanism of CuI-mediated DYKAT appears to involve racemization of the starting material (via a rapidly interconverting allyl iodide intermediate) and CuL* mediated selection of one of the two enantiomers for AAA. In the reaction described here, a related scenario where racemization occurs through an allyl tosylate intermediates seems unlikely as $^{-}$OTs is not generally considered to be nucleophilic, and enantioselectivity increases as the reaction is cooled from room temperature to –40 ºC (Table 2, entries 12, 20 and 21), which would presumably inhibit racemization. It therefor seems more likely that this DYKAT occurs through formation of interconverting allyl-copper intermediates[3a,c,5a] or through enantio-convergent transformations,[5c,f] or a combination of mechanisms. Further studies are required to gain insight.

Conclusions

We have applied alkenylzirconocene nucleophiles in asymmetric allylic alkylation reactions with racemic starting materials to give enantioenriched products. The method is not generally applicable but it does demonstrate that sp^2-hybridized nucleophiles may be used in dynamic kinetic asymmetric transformations. Further experiments are under way.

Notes and references

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† Electronic supplementary information (ESI) available: Materials and methods, procedures, characterization data and spectra. See DOI: 10.1039/c000000x/

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