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Dynamic Kinetic Resolution via Asymmetric Conjugate Reduction: Enantio- and Diastereoselective Synthesis of 2,4-Dialkyl Cyclopentanones

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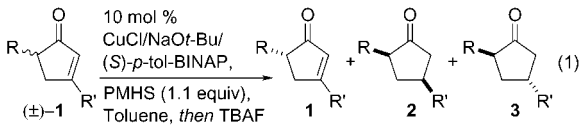
The majority of methods to access chiral β-substituted cyclic ketones employ conjugate addition reactions.[1] Several selective systems have been developed for the asymmetric catalytic conjugate addition of alkylmetals to α,β-unsaturated esters and ketones.[2] We have recently reported that chiral bidentate phosphine complexes of copper (**I**) serve as effective asymmetric conjugate reduction catalysts for enoates and cyclic enones,[3−5] offering a complementary enantioselective method to access such compounds. In this paper, we describe the kinetic resolution[6] (KR) and dynamic kinetic resolution[7] (DKR) of racemic 3,5-dialkylcyclopentenones employing catalytic (*S*)-*p*-tol-BINAP/CuCl/NaO*t*-Bu and poly(methylhydrosiloxane) (PMHS) as a stoichiometric reductant. This process is a unique approach to simultaneously establish two nonadjacent stereocenters in dialkylcyclopentanones (eq 1).



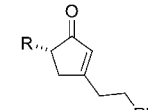
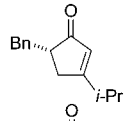
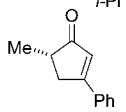
$$s = \frac{k\ \text{(fast-reacting enantiomer)}}{k\ \text{(slow-reacting enantiomer)}} = 25 - 52\ \text{(7 substrates)}$$

The different rates of reaction for the enantiomers of racemic 3,5-dialkylcyclopentenones in the asymmetric copper-catalyzed conjugate reduction enabled us to perform efficient kinetic resolution of these substrates. As is evident in Table 1, high selectivity factors[8] (*s*) were obtained under the kinetic resolution conditions regardless of the alkyl substituent at the 5-position. In cases where primary alkyl and methyl groups were at the 5-position (entries 1, 2, 5−7), the reductions were performed at low temperatures to obtain high selectivity. Notably, high diastereomeric ratios were observed for all reduction products **2** under the KR conditions (dr ≥ 92:8).[9] It is important to note that the kinetic resolution of 3,4-dialkylcyclopentenones gave lower *s* values (<10).

Encouraged by our kinetic resolution results, we sought to extend this method to the dynamic kinetic resolution of 3,5-dialkylcyclopentenones (Scheme 1). We previously postulated[5b] that upon asymmetric conjugate reduction of the enone, a copper enolate[10] intermediate is formed. Subsequent σ-bond metathesis with silane[11] yields silyl enol ether[5b] **4** and regenerates the Cu-hydride catalyst. We reasoned that if the reduction was performed under basic conditions (e.g, NaO*t*-Bu, LiHMDS), rapid racemization of the starting material should occur. Furthermore, since the product ketone is masked as silyl enol ether **4**, epimerization at the α-stereocenter of the desired product would be obviated.

In our initial studies, we determined that the use of amide bases in the DKR resulted in low conversions and poor enantioselectivities. Fortuitously, stoichiometric NaO*t*-Bu could effect the racemization of **1** at temperatures as low as −50 °C. Unfortunately, this epimerization was too slow relative to the rate of conjugate

Table 1. Kinetic Resolution of 3,5-Dialkylcyclopentenones

Entry	1	R	ee (%)[b] of **1** (conversion (%))[c]	s[d]
1[a]		(**1a**) Me	94.6 (55.6)[e]	26
2		(**1b**) *n*-Bu	90.6 (53.2)[e]	27
3		(**1c**) *i*-Pr	97.4 (56.5)[f]	30
4		(**1d**) *t*-Bu	91.0 (50.7)[f]	52
5		(**1e**) CH_2CO_2t-Bu	95.3 (56.0)[g]	25
6		(**1f**)	95.6 (56.0)[e]	26
7		(**1g**)	71.6 (45.0)[e,h]	32

[a] See Supporting Information for the absolute stereochemistry determination of **1a**. [b] Determined by HPLC. [c] Reaction time = 4−12 h. [d] Selectivity factors (*s*) (averages of two or more runs). The % ee and conversion reported are for specific runs. [e] Reaction at −78 °C. [f] Reaction at 0 °C. [g] Reaction at −50 °C. [h] Reaction time = 72 h.

Scheme 1

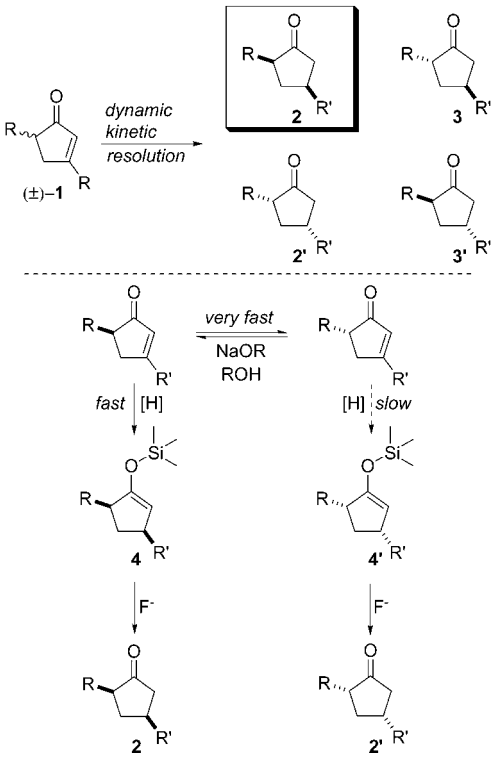


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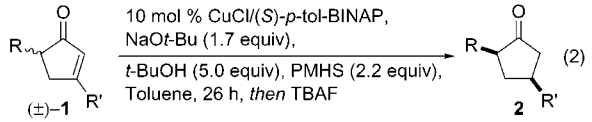
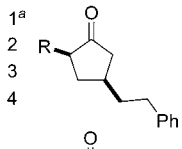
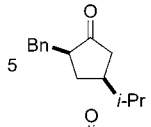
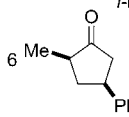
Table 2. Dynamic Kinetic Resolution of 3,5-Dialkylcyclopentenones



Entry	2	R	Yield (%)[b]	*syn:anti* [c]	ee (%)[c]
1[a]		(**2a**) Me	89[d]	91:9	91
2		(**2c**) *i*-Pr	94[e]	93:7	93
3		(**2d**) *t*-Bu	94[f]	93.5:6.5	94
4		(**2e**) CH_2CO_2t-Bu	91[d]	90:10	93
5		(**2f**)	95[d]	91.5:8.5	93
6		(**2g**)	90[d,g]	96.5:3.5	91

[a] See Supporting Information for the determination of relative and absolute stereochemistry of **2a**. Absolute stereochemistry of all other products was assigned by analogy to **2a**. [b] Isolated yield (sum of both diastereomers; average of at least two runs of >95% purity as determined by GC, ^{1}H, and ^{13}C NMR). [c] Determined by HPLC. Average % ee and dr for at least two runs. [d] Reaction at −50 °C. [e] Reaction at −30 °C. [f] Reaction at 0 °C. [g] 3.1 equiv of PMHS and 2.4 equiv of NaO*t*-Bu, reaction time = 48 h.

reduction under these conditions. The addition of *t*-BuOH (5 equiv) as a kinetically labile proton source enhanced the rate of racemization, resulting in the isolation of **2** with high enantiomeric and diastereomeric excesses (Table 2). PMHS proved to be the silane of choice; the use of more reactive silanes (e.g., Ph_2SiH_2) resulted in diminished enantioselectivities. In most cases where the α-substituent was either Me or 1° alkyl, it was necessary to perform the dynamic kinetic resolutions at higher temperatures than the corresponding kinetic resolutions, presumably to achieve efficient racemization of **1** (entries 1, 5−6). In contrast, performing the DKR of isopropyl-substituted ketone **1c** at 0 °C (the optimum temperature for the KR) resulted in a diminished diastereomeric ratio (85:15). We hypothesized that this was due to competitive partial decomposition of silyl enol ether **4** and subsequent epimerization. Thus, lowering the reaction temperature to −30 °C allowed for the clean conversion of (±)-**1c** (94% yield, 93% ee, 93:7 dr). Greater than 95% conversion of the starting material to the desired reduction product was observed in all reactions.

In conclusion, the method we report here represents an example of a dynamic kinetic resolution with simultaneous creation of two nonadjacent chiral centers. The combination of catalytic amounts of CuCl, a commercially available chiral bis-phosphine, and NaO*t*-Bu with PMHS generates a highly enantio- and diastereoselective complex that reacts exclusively via 1,4-reduction. The dynamic kinetic resolution conditions for this catalytic system were achieved by employing stoichiometric amounts of NaO*t*-Bu and *t*-BuOH. Our current efforts are focused on the discovery of new copper complexes that will improve the substrate scope of the asymmetric conjugate reduction as well as mechanistic investigations of this catalyst system.

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Supporting Information Available: Preparation and characterization of all substrates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Selectivity factor, $s = k_f/k_s = \ln[(1 - C)(1 - ee)]/[(1 - C)(1 + ee)]$, where ee is the percent enantiomeric excess of **1** and C is the conversion. For each substrate, comparable selectivity factors (s) were observed at low (24−30%) and at high (45−57%) conversions.

(9) Selectivity factors (s) calculated using the enantiomeric excess of reduction product **2** were consistent with values calculated using the % ee of unreacted **1** for the several cases examined. (In these cases, $s = k_f/k_s = \ln[1 - C(1 + ee)]/[(1 - C(1 - ee)]$, where ee is the percent enantiomeric excess of **2** and C is the conversion.)

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