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Utilization of Molybdenum- and Palladium-Catayzed Dynamic Kinetic Asymmetric Transformations for the Preparation of Tertiary and Quaternary Stereogenic Centers: A Concise Synthesis of Tipranavir

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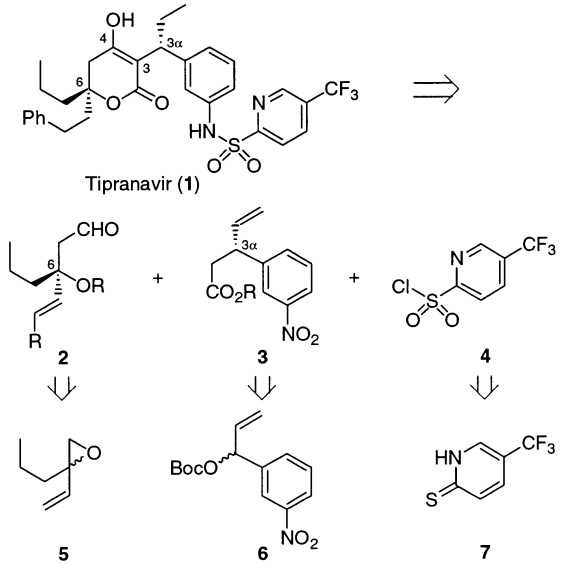
The development of new therapeutic agents to combat the human immunodeficiency virus (HIV) continues to be an intense area of pharmaceutical research. Tipranavir (**1**),[1] a unique, nonpeptidic protease inhibitor (PI) currently in phase IIb clinical trials, has demonstrated remarkable pharmacokinetic properties and offers the significant advantage of oral bioavailability. In addition, HIV-I clinical isolates exhibiting viral resistance to currently available PI agents such as ritonavir, saquinavir, indinavir, and nelfinavir, remain highly sensitive to tipranavir.

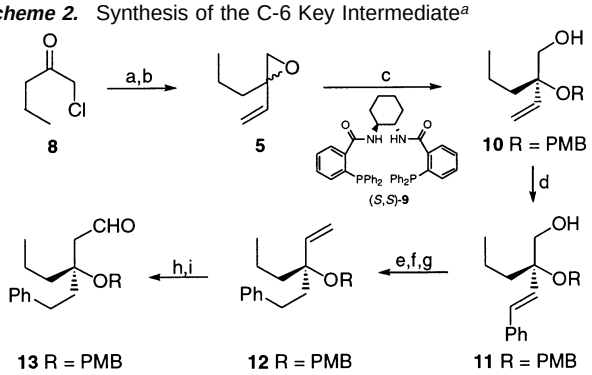
Previous syntheses of tipranavir have utilized either chiral auxiliaries[2a] or resolutions[2b] to obtain the two distally related quaternary C-6 and tertiary C-3α stereogenic centers. In this communication we describe a short and highly efficient enantioselective synthesis of this important antiviral agent based on a double dynamic kinetic asymmetric transformation (DYKAT) strategy. Employing a late-stage pyrone formation approach, it was envisioned that the title compound could be retrosynthesized back to aldehyde **2**, ester **3**, and known sulfonyl chloride **4**[2] (Scheme 1). It was further anticipated that the C-6 key intermediate **2** could be obtained by Pd-catalyzed asymmetric allylic alkylation (AAA) from vinyl epoxide **5**, while the C3α key intermediate could be prepared by a Mo-catalyzed AAA reaction from carbonate **6**.

Scheme 1. Retrosynthetic Analysis of Tipranavir



Synthesis of the C-6 key intermediate started with addition of vinylmagnesium bromide to 1-chloro-2-pentanone (**8**)[3] (Scheme 2). Exposure of the resulting chlorohydrin to NaOH in ether smoothly furnished racemic vinyl epoxide **5** in 86% yield. Subjecting this material to a palladium- and boron-cocatalyzed DYKAT reaction[4] using (*S*,*S*)-ligand-**9** and *p*-methoxybenzyl alcohol as the nucleophile provided allylic ether **10** in a highly regio- and enantioselective fashion (69% yield, 98% ee). Subsequent Heck arylation (10 mol % $Pd(OAc)_2$/40 mol % P(*o*-Tol)$_3$) gave olefin **11** in 92% yield as a single regioisomer. Attempts to install the required phenyl ring via reductive Heck procedures or hydroboration/Suzuki cross-coupling protocols were unsuccessful. Chemoselective hydrogenation of alkene **11** followed by Dess−Martin oxidation and subsequent Wittig olefination provided compound **12** in 93% yield. Rh(I)-catalyzed hydroboration of olefin **12** followed by Dess−Martin oxidation of the resulting alcohol furnished key intermediate **13** in 88% yield (45% yield from ketone **8**).

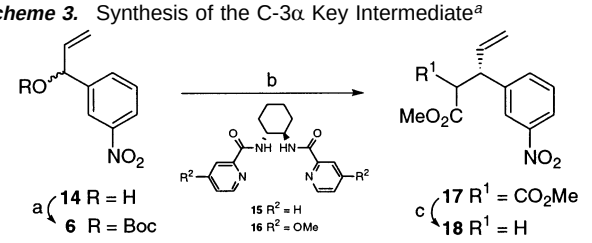
Scheme 2. Synthesis of the C-6 Key Intermediate[a]



[a] Conditions: (a) $CH_2CHMgBr$, THF, 0 °C. (b) 1N NaOH, Et_2O, 25 °C, 86% (two steps). (c) 1 mol % $Pd_2(dba)_3$·$CHCl_3$, 3 mol % (*S*,*S*)-**9**, 1 mol % Et_3B, 1.1 equiv of PMBOH, 69%, 98% ee. (d) PhI, 10 mol % $Pd(OAc)_2$, 40 mol % P(*o*-Tol)$_3$, toluene, Et_3N, reflux, 92%. (e) 5 mol % Pd/C, H_2 (1 atm), MeOH, Pyr, 25 °C, 99%. (f) Dess−Martin periodinane, CH_2Cl_2, 25 °C. (g) $Ph_3P{=}CH_2$, THF, reflux, 94% (two steps). (h) Catechol borane, 1 mol % $(Ph_3P)_3RhCl$, THF then 3 N NaOH, 30% H_2O_2, 25 °C. (i) Dess−Martin periodinane, CH_2Cl_2, 25 °C, 88% (two steps).

Synthesis of the C-3α key intermediate began by treating known allylic alcohol **14**,[5] with Boc_2O in CH_2Cl_2/Et_3N and a catalytic amount of DMAP to provide carbonate **6** in 98% yield (Scheme 3). A key

Scheme 3. Synthesis of the C-3α Key Intermediate[a]



[a] Conditions: (a) Boc_2O, CH_2Cl_2, Et_3N, DMAP, 25 °C, 98%. (b) 10 mol % $Mo(CO)_3(C_7H_8)$, 15 mol % (*R*,*R*)-**15**, dimethy1 sodiomalonate, THF, reflux, 94%, 96% ee. (c) 20:1 DMSO/H_2O, NaCl, 150 °C, 100%.

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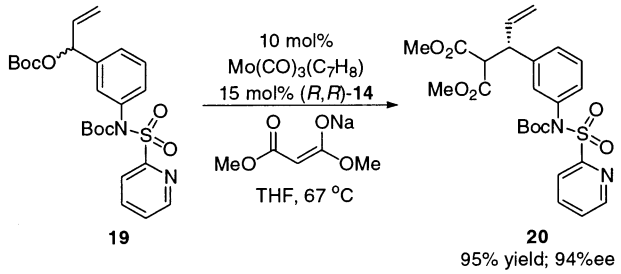
Table 1. Selected Mo-Catalyzed DYKAT Reactions[a]

entry	catalyst	*T* (°C)	*t* (h)	% yield[b]	% ee[c]
1	$Mo(CO)_3(C_7H_8)$/(*R*,*R*)-**15**	67	24	94	96(*R*)
2	$Mo(CO)_6$/(*S*,*S*)-**15**	180[d]	0.33	92	94(*S*)
3	$Mo(CO)_6$/(*S*,*S*)-**16**	180[d]	0.33	94	94(*S*)

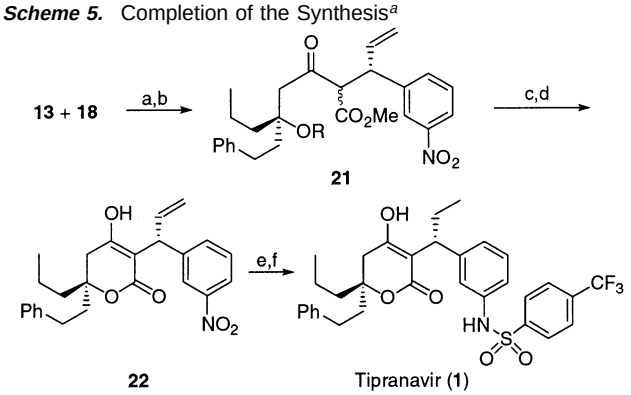
[a] All reactions were performed in THF (0.2 M in dimethyl sodiomalonate) using 10 mol % catalyst and 15 mol % ligand. [b] Isolated yield of the branched regioisomer. [c] Determined by chiral HPLC. [d] Performed under microwave irradiation.

concern in the Mo-catalyzed DYKAT process[6] was the impact of a strongly electron-withdrawing group such as nitro on the regioselectivity of allylic alkylation. Gratifyingly, subjecting compound **6** to the Mo AAA reaction (10 mol % $Mo(CO)_3(C_7H_8)$, 15 mol % (*R*,*R*)-**15**, 2.0 equiv of dimethyl sodiomalonate) furnished the desired branched regioisomer **17** in excellent yield (94%) and enantioselectivity (96% ee) (Table 1, entry 1). Performing the reaction under microwave irradiation[7,8] (180 °C, 20 min) dramatically increased the rate of alkylation with only minimal loss in stereoselectivity (entry 2). In addition, an enhanced efficacy of $Mo(CO)_6$, a more convenient and inexpensive molybdenum source, was observed under such conditions. Utilization of *p*-methoxy-substituted ligand **16**[7] led to a small increase in yield with no effect on enantioselectivity (entry 3). Interestingly, treatment of sulfonamide model system **19** with the standard Mo-catalyzed AAA conditions smoothly provided product **20** in 95% yield and 94% ee (Scheme 4). Failure of the 2-pyridyl moiety in substrate **19** to disrupt the regio- or enantioselectivity of the reaction is noteworthy and suggested that a late-stage employment of the Mo-DYKAT reaction would also be feasible.

Scheme 4. Mo-DYKAT Investigation of Model System



Scheme 5. Completion of the Synthesis[a]



[a] Conditions: (a) NaHMDS, THF, −78 °C. (b) Dess−Martin periodinane, CH_2Cl_2, 25 °C. (89% two steps). (c) CAN, CH_3CN/H_2O, 88%. (d) NaOH, MeOH, 4 °C, 77% (97% brsm). (e) 5 mol % Pd/C, H_2 (1 atm), MeOH, 25 °C. (f) 5-(Trifluoromethyl)-2-pyridinesulfonyl chloride (**4**), CH_2Cl_2, Pyr, DMSO, −25 °C, 92%.

To complete the synthesis, aldol coupling of aldehyde **13** and ester **18** was performed (NaHMDS, −78 °C) followed by Dess−Martin oxidation to give β-ketoester **21** as a 1:1 mixture of C-3 epimers (Scheme 5). After cleavage of the PMB group using standard conditions, pyrone formation furnished compound **22** in 77% yield (97% brsm (based on recovered starting material)). Subsequent hydrogenation and treatment of the resulting amine with 5-(trifluoromethyl)-2-pyridinesulfonyl chloride (**4**)[2,10] provided tipranavir (**1**) in 92% yield.

In conclusion, we have developed a concise, atom-economical[9] synthesis (25% overall yield) of tipranavir (**1**) by employing two highly regio- and enantioselective DYKAT reactions. The current strategy is convergent, starts with commercially available materials, and efficiently addresses the control of two remote stereogenic centers. Moreover, the synthesis highlights the complementary nature of Pd- and Mo-catalyzed AAA reactions.

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Supporting Information Available: Characterization data for compounds **1**, **5**, **6**, **10**−**13**, **17**, **18**, and **22** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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